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HEPARIN IN THE TREATMENT OF ANGINA PECTORIS*

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RECENTLY, while investigating the effect of heparin administration on blood fats, Lyon *et al.*[1] incidentally observed dramatic and uniform relief of pain in 93% of 59 cases of severe angina pectoris. Because of the obvious clinical importance of this observation a study was undertaken to assess this form of treatment using the rigidly controlled technique of the "double blind" test.[2] To comply with this method, the effects of intramuscular injection of heparin and a placebo were compared in each of 20 patients with angina, the identity of the solutions not being disclosed to the patients or to those conducting the investigation. At the completion of the study of intramuscular injections, a few patients were given heparin intravenously.

METHOD

The frequency of anginal pain was used to evaluate treatment. At each visit patients were given a card on which to note each anginal attack and each nitroglycerin tablet used. The cards were carried by the patients at all times, and the importance of recording pain at the time of its occurrence was emphasized. To establish a baseline, no injections were given during the first three weeks of observation, after which "treatment" was administered for a period of six months. "Treatment" consisted of administration of one preparation (heparin or the placebo) for three months followed without interruption by injections of the other solution for three months, reversing the order in alternate cases. The preparations were injected intramuscularly twice weekly in doses of 0.75 or 1.0 ml. so that in the case of heparin each injection contained 75 or 100 mgm., as recommended by Lyon *et al.*[1] The heparin used was concentrated aqueous heparin, 10,000 units per ml.

The placebo and heparin solutions were identical in colour, viscosity, odour and packaging and their identity was withheld from the authors until completion of the study and analysis of the data. None of the patients became aware of the existence of two solutions.

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SELECTION OF CASES

The patients in this study were in attendance at Sunnybrook Hospital and the Toronto General Hospital and the investigation was conducted at these two institutions. From approximately 200 case records of patients with angina pectoris, 30 patients were chosen who fulfilled the following criteria: (1) unequivocal history of angina pectoris; (2) absence of other types of thoracic discomfort, or ability of the patient to distinguish clearly between these and cardiac ischæmic pain; (3) absence of factors which are believed to affect coronary insufficiency, such as aortic valvular disease, paroxysmal arrhythmias, anæmia and diabetes mellitus (patients with congestive failure or recent hæmorrhagic episodes were excluded); (4) willingness to co-operate in regular attendance at the clinic and in faithful tabulation of all anginal attacks. Twenty of the 30 patients selected completed the study; the important findings in these 20 are summarized in Table I.

TABLE I.

THE FINDINGS IN 20 CASES OF ANGINA PECTORIS COMPLETING THE STUDY PERIOD

1. Age	42-73 years, average 57 years	
2. Sex	17 males, 3 females	
3. Duration of angina	4 months to 7 years; average 3 years	
4. Previous myocardial infarction	documentary proof in 13 (65%); suspected but unproven in 2 (10%); apparently absent in 5 (25%).	
5. E.C.G. findings	evidence of coronary artery disease in 12; left ventricular hypertrophy—2; normal in 6 (2 of these had significant changes on 2 step test).	
6. Miscellaneous	Hypertension (180/100 or higher)	6 patients
	Peripheral atherosclerosis	6 patients
	Cardiac enlargement	5 patients
	Chronic auricular fibrillation	1 case

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Ten patients dropped out of the series for various reasons including moving from the vicinity, interference with their work and development of other disorders, such as diabetes mellitus, acute anxiety state, congestive heart failure, cerebral embolism, rectal carcinoma and myocardial infarction. The myocardial infarction occurred in a patient who had been receiving heparin injections for six weeks. These 10 cases are not included in the consideration of the results

RESULTS

All 20 patients said that they had improved at one time or another. Most often they stated they had experienced a reduction in the intensity and duration of the anginal pains and usually it was noticed after the first few injections, regardless of which solution was being administered. Analysis of the recorded pains revealed that 18 patients (90%) had fewer attacks per week during "treatment" than during the initial baseline period. The comparative effectiveness of heparin and the placebo with the control period

TABLE II.

FREQUENCY OF ANGINAL PAIN IN 20 PATIENTS DURING "TREATMENT" PERIODS AS COMPARED WITH CONTROL PERIOD

Number of attacks of anginal pain	*While on heparin*	*While on placebo*
	No. of patients	*No. of patients*
Fewer than during control period	15 (75%)	16 (80%)
Unchanged	3	4
More than during control period	2	0

is shown in Table II: the number of patients benefited by placebo therapy was similar to the number showing improvement on heparin administration.

When the effects of heparin and placebo were compared with each other, there was no appreciable superiority of either in reducing the frequency of attacks of anginal pain per week (see Table III, A). Engelberg[3] noted that the improvement from heparin therapy in patients with angina pectoris may occur gradually over a period of several months and that a time lag of one to eight weeks often elapsed between cessation of treatment and the recurrence of symptoms. To avoid missing such a delayed response, the data were recalculated considering only the last month on each solution. The number of patients who experienced greater improvement from heparin in the third month was not significantly different from those who found more benefit from the placebo (Table III, B).

To determine whether there might be a short period of relief from a possible immediate vasodilator effect of heparin, the frequency of attacks in the 24 hour period after each dose was determined for the last month on each solution (Table III, C). No such effect was apparent.

TABLE III.

COMPARISON OF THE EFFECTS OF HEPARIN AND PLACEBO IN REDUCING THE FREQUENCY OF ANGINAL PAIN IN EACH OF 20 PATIENTS

	A considering the 3-month period on each	*B considering only 3rd month on each*	*C considering only 24 hr. after injection*
	No. of patients	*No. of patients*	*No. of patients*
Heparin superior	7	6	3
Placebo superior	8	7	3
Heparin and placebo equal	5	7	14

UNTOWARD REACTIONS

Reactions to the placebo were few. One patient complained of nervousness, trembling and dizziness after the initial injection of placebo and refused further treatment. Another patient had slight bruising and induration at the site of placebo injections. In the case of heparin, five patients suffered hæmatomas at the injection site. Giant urticaria developed in one patient six weeks after beginning heparin therapy. Sensitivity to heparin was demonstrated by skin testing in this patient; it was overcome by temporarily reducing the size of the injections and administering an antihistamine for two weeks.

DISCUSSION

After the study had been in progress for about three months the identity of the heparin solution was strongly suggested by the occurrence of hæmatomas at the sites of injection of one of the solutions. It could not be ascertained by any difference in relief of anginal pain. The frequency of anginal pain was used to assess the value of treatment since this was considered a

more physiological criterion than electrocardiographic changes or results of exercise tolerance tests. It was also considered that the actual recording of pains was more accurate than the patient's impression expressed as "good" or "bad days".[2] This was borne out by the fact that patients often reported having improved during a particular week, whereas in fact the recorded number of attacks was unchanged.

The familiar but nevertheless remarkable beneficial response to placebos emphasizes the influence of the mental attitude of the patient on the symptoms of severe coronary artery disease. Angina pectoris induces fear in those afflicted which is seldom equalled by any other disease except cancer. In the majority of patients this anxiety is increased still further by personal recollection of one or more episodes of acute coronary occlusion. In a study such as this, repeated examinations by one particularly interested in the patient's disease cannot help but inspire confidence which is augmented by hope for the success of the "new" drug. It is not difficult to understand how the unintentional suggestion accompanying a series of injections can lessen the patient's anxiety and result in symptomatic improvement. It is just as readily apparent how this psychological effect can be a pitfall in uncontrolled studies.

A finding of interest in this study was the fact that 15 of the 20 patients obtained a greater measure of relief during the second injection period, regardless of the order in which the solutions were given. A similar number of patients were started on "treatment" during warm weather and during cold weather, so this response cannot be attributed to climatic changes. Ten of the patients received heparin initially and 10 were given the placebo first. This progressive improvement was also observed by Binder[4] and, while a final explanation cannot be offered, it seems likely that it is an expression of longer exposure to the incidental psychological aspect of the treatment.

Although the alternate use of placebos in testing the effectiveness of heparin in angina pectoris has been criticized,[3] this observation strongly supports this method. Had placebos been used originally in all cases (even for as long as three months), 75% of the patients would have been considered to have greater relief from the subsequent heparin injections and false conclusions might have been drawn.

Apart from the temporary discomfort of hæmatomas there were no serious untoward effects from intramuscular heparin.

INTRAVENOUS HEPARIN

Engelberg[3] found that the best clinical results in angina pectoris were obtained when heparin was given intravenously in doses of 100 mgm. twice weekly. Following the appearance of this report, it was decided to give patients a trial of heparin administered intravenously after they had completed the course of intramuscular injections. No intravenous placebo was used. Seven patients were treated in this manner for periods of from three weeks to three months. Three of these seven patients showed a further slight decrease in frequency of pain, but in no instance was this as great a degree of improvement as that induced initially by the intramuscular injections in these same patients. Three patients showed no change, and one patient had slightly more frequent anginal attacks as compared with the period of intramuscular therapy.

Three of the seven patients had untoward reactions while receiving intravenous heparin. In two, this appeared to be an anaphylactic reaction occurring one or two minutes after the injection during the third week of intravenous therapy. Both patients showed marked flushing of the face, injection of the scleræ and lacrimation. One experienced constricting chest pain which made breathing and speaking difficult for about five minutes. The other patient noticed severe lumbar pain and a pounding occipital headache.

Skin tests, which had been negative a few months before, now revealed sensitivity to heparin in both these patients. The frequency of allergic reactions to heparin in this series is possibly due to sensitivity induced by the long period of intramuscular administration of heparin that preceded the intravenous injections.

The third patient had a sudden hæmorrhage into the right ear drum 20 minutes after an intravenous injection of 100 mgm. of heparin. The resulting deafness improved gradually over the next few weeks. It has been stated that this dose of heparin is quite safe.[3] While this is generally true, it is well known that for an hour or so after such a dose the whole blood clotting time is usually prolonged from the normal of 10-12 minutes (Lee White) to one or several hours. The risk of bleeding during this period should not be overlooked.

TABLE IV.

SUMMARY OF REPORTS ON HEPARIN IN ANGINA PECTORIS

Author	No. of cases	Dose of heparin	Duration	Comments	Results
1. Lyon *et al.*[1]	59	50 to 100 mgm. i.m. or i.v. once or twice weekly.	1- 8 months	Placebos afterwards in 7 cases.	55 improved on heparin; none improved on placebo.
2. Engelberg[2]	29	25 to 100 mgm. i.m. or i.v. twice weekly.	6-12 months	Placebo controls first in 11 cases.	55% improved on heparin.
3. Zinn *et al*[3]	14	100 mgm. i.m. three times weekly.	6 weeks	Double blind control	Placebo just as effective as heparin.
4. Binder *et al*[4]	34	100 mgm. i.v. twice weekly.	1 month	Double blind control	Placebo just as effective as heparin.
5. Rinzler *et al*[5]	18	100 mgm. i.v. twice weekly.	8-9 weeks	Double blind control	Placebo just as effective as heparin.
6. Gruner *et al*[7]	27	100 mgm. i.v. twice weekly.	7-11 weeks	Placebos, then heparin, then placebos.	9 improved on placebo; 6 improved on heparin.
7. Port *et al*[8]	13	75 mgm. i.v. twice weekly.	10 weeks	Four alternating 10-week courses of heparin and placebo.	Placebo just as effective.
8. Russek *et al*[9]	14	50-100 mgm. i.v.	1 to 7 injections, 1 to 3 days apart.	No placebos	Subjective benefit in 3; no significant changes in 2-step test.
9. Present series.	20	75 to 100 mgm. i.m. twice weekly.	3 months	Double blind control	Placebo just as effective as heparin.

Since this study was undertaken, additional reports on the use of heparin in angina pectoris have appeared. These are summarized in Table IV. The majority of these show results similar to those in the present series.

SUMMARY

1. Under controlled conditions, the effectiveness of heparin administered intramuscularly in reducing the frequency of pain in 20 cases of angina pectoris was no greater than that of the placebo.

2. In this study, as in others, the psychological benefit from a new form of treatment of angina pectoris was striking.

3. Intravenous heparin was administered to seven patients with angina pectoris following the course of intramuscular injections. No appreciable improvement was noted.

4. Side effects of intramuscular and intravenous heparin were observed occasionally and are described.

The heparin and placebo used in this study was prepared and supplied by The Connaught Medical Research Laboratories, University of Toronto. Dr. R. Ian Macdonald made available to us facilities of Sunnybrook (D.V.A.) Hospital, Toronto, where part of this study was carried out.

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RÉSUMÉ

Les auteurs de cette communication ont cherché à reproduire les résultats obtenus par Lyon et Yankley, dans le traitement de l'angine de poitrine par les injections d'héparine. Les vingt malades traités accusèrent une amélioration à une phase ou à une autre du traitement; 90% eurent moins d'attaques par semaine pendant la durée du "traitement" qu'au début, sans égard au fait qu'ils aient reçu de l'héparine ou une substance inerte ayant l'apparence de l'héparine.

Comme on avait déjà rapporté, dans le passé, que l'amélioration produite par l'héparine peut être tardive et ne se manifester qu'après une période de plusieurs mois, l'expérience fut répétée en tenant compte seulement des données obtenues pendant le dernier mois de traitement avec chaque produit. Le nombre de malades améliorés par l'héparine était sensiblement le même que celui des cas soulagés par la substance contrôle. Celle-çi ne produisit que de rares effets fâcheux. Par contre, cinq malades traités à l'héparine firent des hématomes dans la région des injections. Un patient sensible à l'héparine présenta un urticaire géant six mois après le début du traitement.

L'amélioration apportée par une substance quelconque sert à démontrer, une fois de plus, l'importance de l'attitude mentale des angineux vis-à-vis de leurs symptômes. L'amélioration progressive notée au cours de la deuxième série d'injections montre l'effet d'une diminution de l'angoisse du malade et d'une augmentation de confiance en son médecin.

L'administration intra-veineuse d'héparine telle que recommandée par Engelberg donna des résultats encore moins satisfaisants que par voie intra-musculaire. Le risque d'hémorragie dans l'heure qui suit l'injection de 100 mgm. d'héparine dans la veine ne doit pas être perdu de vue.

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CATAPLEXY AND OTHER RELATED FORMS OF SEIZURE*

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IN 1880 GÉLINEAU published his classic paper describing a number of patients presenting two kinds of attack. The one took the form of sudden, overpowering drowsiness and sleep during the day, usually of brief duration. This kind of attack had been previously described and called narcolepsy. The other was an attack of weakness or paralysis precipitated by emotion, again sudden and invariably brief. To this second variety of seizure the name cataplexy was given. Later writers have, as it appears to me, created confusion by subsuming both varieties of attack under one heading and using the term narcolepsy to describe Gélineau's syndrome. They take narcolepsy to include both sleep attacks and cataplectic attacks. This is inaccurate and misleading for, as has been pointed out by many others before, either form of seizure may occur alone. Narcolepsy is a correct and convenient term for the sleep attacks, and cataplexy for the others; it is in this sense that I shall use them, referring to the association of the two as Gélineau's syndrome.

Cataplexy is, of course, far more often observed in Gélineau's syndrome than in any other context, and cases of this syndrome are commonplace in neurological practice. I shall nevertheless venture to remind you of its main features, which can be stated simply. The patient, who is otherwise in good health, is liable to attacks of overpowering drowsiness leading to sleep during the day. These are most likely to occur during inactivity, or after a meal, but may occur at any time, for instance, during conversation or while eating. The duration of sleep is variable—from ten minutes to an hour or two. Nocturnal sleep is normal. The other complaint is of sudden loss of power caused by vivid emotion, and especially by laughter. The duration of these attacks is always brief. They last from a few moments to a minute or two. Their severity varies from a sense of weakness to complete collapse, so that the patient falls if standing. Apart from laughter or amusement, other pleasurable emotions are usually the most effective precipitants—the excitement associated with a winning stroke at tennis, or raising a gun for a good shot at a bird. One of my patients, a young and active man, said he had had to give up playing all games because any thrill would make him "go flop". For laughter to be effective there must be genuine amusement. A patient said to me that when he told a funny story and laughed he always had an attack, but not always when he laughed at someone else's story. Of the non-pleasurable emotions, annoyance is most often blamed. It must be a sudden surge of feeling. A patient of mine ran to catch a bus in the rain, and as he almost reached it the conductor rang the bell and it moved off. He fell helpless in the muddy road, overcome by his emotion. Of all the emotions, however, laughter is the most effective, and in some of my own cases it has been the only precipitant of attacks. This specificity of trigger mechanism is remarkable, and I will allude to it again later.

Rarely cataplexy may occur without the coexistence of narcolepsy, but in these cases, so far as I am aware, it is not laughter, but some other emotion which is the usual precipitant. One of the best examples is that recorded by Gordon Holmes (1927), in a patient whom I was privileged to see on several occasions while he was in the National Hospital, Queen Square, London. This was a boy of 14, who since the age of five had been subject to falling on noise or surprise. Any loud sound, such as a tire bursting, a motor hooting, or a door slamming, might cause him to fall; surprise had a similar effect. For example, being overtaken silently by a cyclist when walking, a cat jumping on to the table, or being touched from behind might cause him to fall, sometimes so abruptly that he had suffered many fractures of his limbs. There was never any degree of loss or disturbance of consciousness, no change of colour, and no vertigo. At first while he was in the ward it was easy to produce a fall by a sudden noise, but he became expectant and, the element of surprise being removed, the stimulus was no longer effective. There had, it seemed, to be a certain affective quality in the stimulus. While in hospital he had a single epileptic attack in his sleep. In this he was cyanosed, his limbs were convulsed and his eyes deviated to the right. This case at once raises the question of the relationship of cataplexy to epilepsy, which has been much disputed. Adie (1926) considered Gélineau's syndrome to

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be a disease *sui generis*, having nothing to do with epilepsy. Wilson (1928), from his own observations, arrived at the opposite conclusion, and confirmed this opinion in his textbook (1940). Before giving my own views on this subject I shall present some further observations.

Although the constituent features of Gélineau's syndrome are remarkably constant in nearly all cases, there are exceptions which deserve careful consideration. Thus in some instances, otherwise typical of the syndrome, attacks of powerlessness may occur without any precipitating cause, being in all other respects like the usual cataplectic attacks. On account of this spontaneous character they need a separate name, but for convenience of discussion I shall refer to them as spontaneous cataplexy. The following case provides an illustration.

CASE 1

A married woman aged 27 had begun a year previously to have attacks of sudden, unaccountable drowsiness in the day so that she would fall asleep even while eating a meal. A little later she began to have sudden falls. Without warning, her legs would give way and she would flop and have to stay on the floor for half a minute. If sitting, she would be quite unable to move or speak and her eyes would close, though the attacks were so brief that they often passed unnoticed by others. They might also occur in bed. There was no disturbance of consciousness, and she had a clear appreciation of her surroundings throughout the attack. She was emphatic that these attacks usually occurred without any cause so far as she could determine, but on one or two occasions she had noticed an emotional precipitant. The examples she gave were, sudden apprehension, if she saw something unpleasant about to happen, or if she were excited at an unexpected meeting with an old friend. Such occasions, however, were exceptional. As a rule the attacks were spontaneous.

Examples of spontaneous cataplectic attacks have been recorded by others (Wilson 1928, Rothfeld 1938). Wilson (1928) was also the first to draw attention to the resemblances of cataplexy to sleep paralysis. This condition was first described by Weir Mitchell (1897), who called it nocturnal paralysis; but, as attacks may also occur in the day, sleep paralysis is the better term. They may happen either at the moment of going to sleep, or during sleep, and have accordingly been divided by Levin (1933) into pre-dormitial and post-dormitial paralysis; but sleep paralysis covers both forms. In these attacks the subject is perfectly conscious, but unable to move, the paralysis lasting for a minute or two. The paralysis is as a rule complete, the patient being unable to speak. This uncommon affliction is not as a rule associated with other symptoms, but may occur in association with Gélineau's syndrome. The following case provides an example and at the same time introduces another rare feature of the syndrome, forms of attack which are intermediate between narcolepsy and cataplexy.

CASE 2

The patient was a serving officer aged 29, seen during the war. He had had no illness of note before the present illness began. The first episode occurred during coitus, when at the moment of orgasm he experienced a sudden collapse. All his muscles went completely limp, his jaw dropped, his head fell forward, and he was unable to speak. The whole episode lasted about a quarter of a minute and he then felt quite well.

Two days later he was just going off to sleep and suddenly found himself paralyzed. He was unable to move any part of his body. The attempt to speak resulted in an inarticulate sound. The attack was over in less than a minute. Subsequently he continued to have these attacks at frequent intervals just as he was going off to sleep, either at night or if he dozed during the day. He next developed a typical Gélineau's syndrome—attacks of irresistible sleep during the day and a liability to collapse on excitement. Joking and laughing in the mess would bring these on, "especially if I make the joke rather than others". He had once fallen on a tennis court when about to deliver a smashing volley. He still occasionally had a collapse in coitus. He would also have collapses for no apparent reason. He found, moreover, that if he was feeling tired and sleepy and gave way to this feeling, he might have a collapse instead of going to sleep. Even the thought of relaxing might cause this. He gave an example. Going on leave after a long walk through streets he entered a lift in a hotel, in which there was a seat. The thought of relaxing and sitting down at once made him crumple up. There was no sleepiness.

The opposite occurrence, attacks of sleep precipitated by emotional excitement, has also been recorded (Wilson 1940), though I have not observed it personally.

The resemblance of spontaneous cataplexy to a certain variety of epilepsy, so-called akinetic epilepsy, is obvious. Akinetic epilepsy is a term now used a good deal for seizures in which the outstanding event is a fall, and it is indeed worth enquiring why some patients in minor attacks fall and others do not. The fall does not appear to depend upon loss of consciousness. Some patients in their attacks are unresponsive and apparently unconscious without falling: others fall with only a momentary arrest of thought, and others again (so far as can be observed) without any loss of consciousness at all. Falling in minor epilepsy may, of course, result from widespread muscular spasm, and this may be so brief that it is observed with difficulty. Natter and Gastaut (1950) suggest that this is the true interpretation of the so-called akinetic attacks which Lennox (1951) and others include in their symptomatic triad of juvenile petit mal. According to this view, there is a sudden, momentary, generalized, myoclonic shock which throws the patient to the

ground. This interpretation may be correct, but it is certain that in some epileptic seizures falling is due to momentary loss of muscular action. Whether there is interruption of consciousness in attacks of this kind is difficult to ascertain, but from the introspection of patients I am satisfied that falling with no disturbance of the senses does occur. Ramsay Hunt (1922) deserves the credit of recognizing such attacks, and of coining for them the descriptive term "drop seizures". My own impression is that drop seizures are rare, that they occur not in association with frank epilepsy, but as an isolated phenomenon, that they are usually met with in women past middle-age and that a family history of the complaint is not uncommon. I have notes only of four cases in my private records, but have certainly seen an equal number in hospital practice. The story of the attacks in each instance has been the same and may be illustrated by the following account given me by a woman aged 62.

CASE 3

The first of her attacks had occurred in her early thirties (my impression being that this is an unusually early age of onset). Thereafter she had had them infrequently until recently. She might be free for several months and then have two or three in the course of a fortnight. There had been five in the five weeks before I saw her. The onset was sudden and unexpected, her legs gave way and she fell forward on to her hands and knees. She was certain that there was no disturbance of consciousness. She was able to put her hands out to save herself, but would occasionally bruise her knees. There was no giddiness. She was able to pick herself up immediately. Her husband, who had witnessed many attacks, confirmed her account, being certain that there was no jerking or twitching of the limbs, nor any loss of consciousness. The attacks occurred only when she was walking. They were never precipitated by laughter or sudden emotion. The patient clearly remembered that her mother at the age of 55 began to have exactly similar attacks and continued to have them occasionally until she died 10 years later. The patient had witnessed these attacks, but not until after she herself had had them. A sister of the patient, two years older, had similar attacks, the age of onset in her case being uncertain.

In their paroxysmal character and stereotyped pattern, these drop seizures clearly resemble epilepsy. The fact that there is no disturbance of consciousness is, of course, no objection to their inclusion in this category, for focal discharge without disturbance of consciousness is a well known occurrence. Indeed, momentary paralysis of a more obviously focal character without any attendant disturbance of the senses is well recognized. A man at present under my care with a right parietal tumour has momentary attacks in which his left arm goes limp and he drops whatever he may be holding in the hand. There is no twitching and no paræsthesiæ, and between attacks he has little disability in the limb. These inhibitory motor seizures have been described by Holmes (1927) and others. The rarity of their occurrence requires explanation, but they may be reasonably accepted as epileptic; in this connection it is noteworthy that in cataplexy, in the attacks which I have called spontaneous cataplexy, in sleep paralysis, and in drop seizures the paralysis has been observed at times to be partial or asymmetrical. It would seem, therefore, that cataplectic attacks may represent only a wider distribution of the focal inhibitory motor epilepsy which may be observed in a single limb.

There is another point of resemblance between cataplexy and epilepsy—the reflex nature of the attacks. Reflex epilepsy, that is to say seizures clinically recognizable as epileptic and induced by specific stimuli, has been long known and much discussed. Noise, startle, sexual orgasm, and the act of micturition are among the stimuli known to precipitate attacks in certain subjects. The act of coughing may also induce attacks. This has been questioned owing to the fact that violent and prolonged coughing may cause unconsciousness and clonic convulsions from cerebral anoxia (Baker 1949). This doubtless accounts for most of the cases of so-called laryngeal epilepsy reported in the past, but there are some in which the cough is no more than a tickle and could not cause cerebral anoxia. I mention the point because it is relevant to the interpretation of a case to be described presently.

Of the precipitants mentioned, startle and noise are the most common, and sometimes are effective only in combination. But startle alone may induce attacks in some persons, and then quite often. Thus one epileptic patient under my care would have attacks induced by stubbing his toe against an obstruction when walking in the dark, another under the same circumstances by the sudden and unexpected passage of a cyclist from behind. Cases have also been observed of epilepsy precipitated by laughter. Thus there is a considerable body of circumstantial evidence for a clinical affinity between cataplexy and epilepsy. I have two unrecorded cases to present which add to this evidence:

CASE 4

A service man, aged 40, was referred for specialist examination for dozing off to sleep at odd times and attacks of paralysis.

A maternal uncle was epileptic. He himself had had no illness apart from a tuberculous hip in boyhood and

the symptoms now to be described, which fall into three distinct phases. In his childhood he was subject to what were called fainting attacks if he hurt himself (for example, if he cut his finger) or if he were upset (for example, if he saw a dog run over) or if he lost his temper. Things went black, and he would fall to the ground unconscious. He was not told of any convulsive movement. This liability continued up to the age of 16. At 15, while standing to watch a procession, without any emotional precipitant, he had a faint in which a companion observed jerking movements of the limbs, and in which he wet his trousers. This was the first phase. The story is that of frequent fainting on emotion, ending with a fit; this sequence has often been observed and discussed without any explanation other than that the excessive liability to fainting and the liability to epilepsy are separate manifestations of an inferior nervous system.

The second phase lasted from the age of 16 to 35, during which period the only occasions on which he lost his senses were when he got up at night to pass water. There would usually be some urgency about this, but the faint would not occur until he had got to the lavatory and commenced to pass water. Things would go black, and he would lose his senses and fall. He had occasionally hurt himself in falling. After one of these faints he would have a headache and feel shaky. Attacks of this kind are uncommon; but I have collected a dozen cases, all in males, with exactly the same story, none of them, however, with any other symptoms. I have regarded them as a species of reflex epilepsy.

The third phase began when he was 35; while washing in the morning he suddenly fell to the ground without any blacking out of vision or loss of senses. His mouth dropped open: he could not move his limbs: he could open his eyes only with a great effort. This lasted only a few seconds, after which he picked himself up and felt quite well again. Eighteen months passed without incident and he then began to have typical attacks of cataplexy, provoked by amusement, anger, pleasurable excitement or sudden noise such as gunfire. The liability increased so that the attacks would occur with little provocation, and he would have as many as six in a day. He noticed at the onset quivering of the jaw. An attack was witnessed by a nurse and described as follows. He was talking normally when a comrade threw a box of matches to him. He then seemed to lose all use of his limbs and fell with chin sagging loosely. His eyes were partly closed as if he were trying to open them, but he could not manage it. At the onset his face generally twitched.

In the past year or two he had also had attacks on waking from sleep, either in the night or day, identical with the attacks of paralysis during waking hours. And finally, for four years he had had an increasing liability to drop off to sleep in the day time. The description of this was characteristic of narcolepsy. The sleep attacks were of sudden onset, and one had occurred when he was driving a car, his wife saving him from disaster by taking the wheel.

I have found no parallel for this case either in my own experience or in the literature, but present it as suggesting a link between cataplexy and reflex epilepsy.

The next case is also important in this connection.

CASE 5

A quartermaster-sergeant aged 35, a regular soldier with 13 years' service, came with the symptoms and signs of syringomyelia, which had been present for about four years; for the same period he had been subject to the attacks which will be described. It should be recorded that his mother was an undoubted epileptic, and that his paternal grandfather and grandmother had both died insane.

The first of his attacks was spontaneous. He fell unconscious without warning and recovered his senses 20 minutes later, having bruised the back of his head. Subsequently he found himself liable to attacks of a peculiar kind if he laughed with real amusement, or was startled by a sudden noise. There was also a particular liability to attacks at the moment of going off to sleep if his wife spoke to him or anyone came into the room. In most of these attacks he lost his senses and his wife told him he was convulsed, though there was no tongue biting or incontinence. But in some of the attacks precipitated by laughter or sudden noise he might collapse, and if unsupported fall, without loss or disturbance of consciousness. He appeared to have some warning of an affective kind and stated that if at this moment he exerted control he could prevent loss of consciousness. When he did lose consciousness he was told that he was always convulsed. He also had attacks which began with a cough and ended in a fit. In the past eight months, in coitus, after ejaculation he had had an attack of coughing which went on to a fit, this sequence being invariable.

There were no attacks of narcolepsy or sleep paralysis in this case.

Here, therefore, we have a patient whose first symptom was what appears to have been a spontaneous epileptic attack, and who subsequently had attacks which might take the form either of cataplexy or reflex epilepsy, their form being determined by the opportunity of exerting that volitional control which we know to be often effective in preventing the spread of epileptic discharge. From these observations I conclude that cataplexy and the other related forms of seizure (spontaneous cataplectic attacks, drop seizures, falling on noise or surprise, and sleep paralysis) may be considered as epileptic variants, having a common focal region of discharge. Looking for some comparable epileptic manifestation, I believe we may find an analogy in myoclonic seizures. These, as is well known, may be precipitated by sensory stimuli. A visual stimulus in the form of flicker is the most effective, but one may observe patients in whom a touch or noise will suffice to provoke a myoclonic spasm, if it is unexpected. I have found a patient who could invariably be thrown into a spasm by a surreptitious kick against the foot of his bed. There is one group of myoclonics in which there is another curious resemblance to Gélineau's syndrome. These are patients who are subject to myoclonic jerks just as they are dozing off to sleep, or even if they relax during the day. They are then roused by a sudden involuntary jerk, repeated when they doze off again, and such repetition may continue to an extent which prevents sleep for an hour or two. In these patients myoclonus may also occur during sleep and awake them, but they very rarely have attacks which go on to loss of consciousness or convulsions. We find, therefore, in the analysis of myoclonic epilepsy features which in some respects resemble

attacks of the cataplectic and narcoleptic type, and we may in this respect regard paralysis and myoclonus as corresponding opposites.

The close association of narcolepsy and cataplexy, and the observation of intermediate forms, are of some physiological interest. Flaccid immobility and normal sleep are naturally associated phenomena. It would not be surprising, therefore, if the functional centres controlling these two phenomena were closely associated in the brain. The patient, whom I have mentioned as having paralytic attacks when he became drowsy and relaxed, remarked that it seemed to him as if his body went to sleep without his mind. Another patient with sleep paralysis said that his mind appeared to wake up without his body.

One of the striking things about patients with cataplexy is that they do not lose consciousness and are not convulsed. The case I have recorded, it is true, provides an exception to this rule, but it is a rule that is almost absolute. If cataplexy is an epileptic variant the discharge is one that does not spread. Little is as yet known of the physiological factors which inhibit or facilitate the spread of epileptic discharge, but the occurrence of circumscribed discharge is well recognized in experimentally induced seizures. It may depend upon anatomical factors. If cataplexy is the clinical expression of an epileptic discharge arising in deep-lying structures, for example, in the periaqueductal grey matter, with little opportunity for outflow to the cortex we might expect to find consciousness intact, absence of convulsive movement and a normal electroencephalogram, as in fact we do.

I have mentioned the reticular formation of the brain stem as a possible site for the discharge responsible for flaccid immobility. This speculation is not new, being derived from the observation of Gélineau's syndrome as a sequel of encephalitis lethargica, in which the main incidence of the disease is in this region. There is evidence also from cases of tumour supporting the existence of functional localization in this area for control of sleep and waking, and for maintenance of postural tone. Kelly (1951) in his analysis of the symptoms in 29 cases of colloid cyst of the third ventricle found six in which there were attacks of sudden falling described thus: "There is a sudden paresis of both lower limbs apparently without any interference with the state of consciousness. The patient suddenly collapses to the ground and is usually unable to rise again for a few seconds." I have observed similar attacks in two cases of suprasellar tumour.

Ethelberg (1950) has described, under the title symptomatic cataplexy, attacks of the same kind in two cases of depressed fracture with pressure upon the lateral surface of the frontal lobe, and has drawn attention to other cases in which the lesion was supratentorial. These, as he remarks, are to be distinguished from attacks in which flaccid immobility is confined to a single limb, yet the underlying mechanism may be the same. If there are centres, in the Jacksonian sense, in the brain stem for the maintenance of motor activity, one would expect this function to be re-represented at cortical level and in relation to different parts of the body. In other cases of generalized cataplectic attacks Ethelberg has noted cortical lesions affecting the mesial surface of both frontal lobes. In all these cases the cataplexy was of the spontaneous kind. The attacks were in fact drop seizures. Stoupel (1950) states that in three patients with true akinetic epilepsy he has observed electroencephalographic signs of focal discharge on the mesial surface of one hemisphere.

To sum up, clinical observation suggests that there is no fundamental distinction between epilepsy and cataplexy, and that other types of seizure related to cataplexy are also epileptic variants. There is reason for supposing a natural physiological association between flaccid immobility and sleep which might explain the frequent occurrence of cataplexy and narcolepsy in the same patient. Such evidence as is provided by pathology suggests that the discharging lesion resulting in the symptom of transient flaccid immobility is usually in the brain stem. There is further evidence suggesting that transient flaccid immobility, either of a generalized or partial character, may result from epileptic discharge in the cerebral cortex.

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SOME STUDIES WITH LARGACTIL*

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DURING the past 18 months, much has been heard concerning the beneficial effect of the drug Largactil (chlorpromazine) when given in a variety of circumstances.[1 to 4] Benefit has also been recorded when it has been used in conjunction with other drugs.[5] Its administration to patients in shock has been reported in both the medical and the lay press.

Laborit and Huguenard have made considerable study of the response of the autonomic nervous system to a variety of stimuli, and have shown interest in the exhibition of drugs which might depress the deleterious responses of this system.[7]

The drug Largactil belongs to the Diparcol-Phenergan series, the actions of which it includes. It is said that Largactil causes depression of parasympathetic and sympathetic impulses and that the ganglia are depressed. It is stated to be antihistaminic, to have a potentiating effect on drugs which themselves depress the central nervous system, and to affect the temperature-regulating mechanism.[5]

This drug for which such qualities are claimed, attracted the attention of the Department of Anæsthesia of the Queen Mary Veterans' Hospital. Before giving it widespread clinical trial, however, more knowledge of its action was thought to be desirable, particularly of its action alone rather than in combination with other drugs. Accordingly, by means generously afforded by the Research Division of the Department of Veterans' Affairs, the aid of a Fellow in Anæsthesia (A.B.D.) was enlisted, to help work out some of the problems.

PRESENT STUDIES

The studies were divided into four groups: (1) The response of the normal healthy adult to the administration of a single intravenous injection. (2) Certain responses of the anæsthetized individual. (3) The use of Largactil in peripheral vascular disease, in intractable pain, and in altering gastric secretion. (4) Animal studies. Some of these overlapped each other.

1. PHYSIOLOGY

A number of physiological studies were carried out on seven volunteers. The average dose was 1.5 mgm. per kgm. body weight intravenously. It was diluted with water to 20 ml., then injected into the tubing of a pre-existing intravenous drip of 5% glucose and water. This latter precaution was considered necessary to avoid local irritation.

The results of these tests were uniform and are summarized below. (a) *Blood.*—Sodium, potassium, chloride and phosphate levels and pH were unchanged; bicarbonate level fell moderately. Oxygen content and carbon dioxide content were stable. Hæmoglobin concentration and hæmatocrit values were unaltered. Blood sugar level rose appreciably, and blood urea level fell significantly. (b) *Cardiovascular system.*—The blood pressure became orthostatic, the pulse rate showed a moderate rise, and the ECG showed frequent sinus arrhythmia. (c) *Respiratory system.*—Tidal volume was diminished, this depending on the size of dose. The average fall for a 25 mgm. dose was from 530 to 414 ml. Respiratory rate varied, usually it was slightly increased while in some cases respiration became irregular. Oxygen consumption was slightly increased, the average rise for a 25 mgm. dose being from 248 to 268 ml. a minute. (d) *Central nervous system.*—The EEG interpreted by Dr. D. Lloyd-Smith, showed a sleep pattern. Arousal from this was rapid, as there appeared hyperactivity to stimulation. Following postural hypotension there was evidence of cerebral anoxia. The pupils were constricted. Muscle strength, as demonstrated by the dynamometer, fell rapidly.

2. ANÆSTHESIA

Pulmonary ventilation studies were performed on 14 patients, in whom medium-level to low spinal anæsthesia was induced.

These patients were given oral premedication with Largactil alone; a 150 mgm. dose was given the previous evening and 50 mgm. was given intramuscularly one hour before operation. Light sleep was produced with nitrous oxide and oxygen at a fifty-fifty concentration. Pulmonary ventilation was then observed over a 30-minute

*Synonyms: Chlorpromazine—Thorazine—Poulenc R. P. 4560.

Generous supplies of this drug were graciously given by Poulenc Ltée, Montreal.

From the Department of Anæsthesia, Queen Mary Veterans' Hospital, Montreal.

period by means of a Thomas dry gas displacement meter. Largactil 20 mgm. was then given intravenously and the ventilation observed over a similar period. The respiration rate then remained normal or showed a slight rise. Tidal volume fell from 435 to 315 ml., and minute volume fell from 8.75 litres to 6.9 litres.

In *premedication studies* 164 patients were closely observed, these undergoing a variety of operations. The ages of the patients varied from 18 to 78 years. The average dose was 150 mgm. by mouth the previous night and 50 mgm. intramuscularly one hour before surgery. Multiple observations were made along the lines of those of Cohen and Beecher,[8] so that comparison could be made with this work.

On reaching the operating room the patients were calm and disinterested. Their skin was often pale, warm and dry. Their pupils were constricted and they were weak. The pulse rate was slightly raised and the blood pressure was usually slightly lowered. Salivary secretion was absent. Induction of anæsthesia was smooth and intubation simplified. During operation, a much smaller quantity of the agents was necessary to maintain anæsthesia. This was common to general anæsthesia, spinal anæsthesia or regional block. When the usual amounts were given with any of these three types anæsthesia was prolonged.

Postoperatively these patients were quiet, relaxed and easily controlled; they needed less medication. Hypotension, when it occurred, responded to posture, infusions and application of pressure bandages. Postoperative nausea or vomiting was rare, occurring mildly three times in this mixed group. Only one unusual symptom was observed, incontinence of urine, which was present in 4% of the cases.

3. THERAPY

(a) *Peripheral vascular disease.*—Because of the marked peripheral vasodilatation which follows the use of this drug, a number of subjects with and without peripheral vascular disease were investigated with a multipolar thermocouple. It was clearly demonstrated that the rise in the skin temperature of the extremities was equal to that induced by either spinal anæsthesia or sympathetic block. It appeared to surpass that initiated by other vasodilator drugs.

The temperature response was found to be equal to that described by Barcroft,[9] which occurs following sympathectomy and which gives rise to a maximum blood flow. Sublingual, rectal and intramuscular temperature fell by 1 to 2 degrees Centigrade during one hour.

Peripheral vascular diseases studied included frostbite and acute embolism, clinical occlusive disease, and proven Buerger's disease. These studies are continuing.

(b) *Intractable pain.*—There has been opportunity to use Largactil on patients suffering from the pain of inoperable cancer. Patients previously receiving larger and oft repeated injections of opiates or similar drugs have responded favourably to Largactil plus aspirin, phenacetin and codeine, Largactil plus a small dose of codeine, or Largactil plus a small dose of Demerol, such medication being given very much less frequently, and usually only three times a day.

(c) *Gastric secretion.*—Five patients were studied. It was found that gastric secretion was depressed by Largactil, but that a marked response to insulin remained. This suggests therefore that the depression is not a simple vagolytic response.

A few cases of painful gastric ulcer have been given Largactil out of interest. This has resulted in complete relief of pain.

4. ANIMAL EXPERIMENTS

The work of Professors F. C. MacIntosh and K. I. Melville at McGill is being closely watched by members of this department. It has been our privilege to observe or take part in a number of their studies.

It appears that Largactil may antagonize in some way the action of adrenalin (epinephrine), noradrenalin, acetylcholine and histamine, but there appears to be no effect upon the myoneural junction. The antiadrenergic effect of Largactil in chloroform-adrenalin sequence in the dog is truly remarkable.

CONTRAINDICATIONS

From other evidence at hand, it appears that Largactil should not be given in the presence of acute or chronic liver disease, or when there is respiratory depression.

CONCLUSIONS

1. Largactil has very interesting potentiality; more has yet to be discovered concerning the site and mode of its action and its toxicity when given over long periods.

2. It appears to be of value as a premedicant, especially in patients undergoing operation under regional anæsthesia.

3. When it is used in premedication, the incidence of postoperative vomiting is extremely low.

4. The results of diagnostic and therapeutic use of Largactil in peripheral vascular disease, are most impressive.

5. It would seem to be of great use in anæsthesia for the poor-risk case in which normal quantities of anæsthetic agents are contraindicated.

6. By virtue of the peripheral vasodilation which follows its use, hypothermia may be facilitated, if that is desired.

7. It may be of use in some types of "shock", but more evidence must be forthcoming to prove that in these vasodilatation is preferable to vasoconstriction.

Thanks must be recorded to Dr. A. H. Neufeld, Dr. Hugh Starkey and their respective staffs for facilitating our studies and for giving advice concerning numerous details.

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TREATMENT OF PARALYSIS OF THE EXTRA-OCULAR MUSCLES*

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THE OPINION persists in some quarters that surgery can do little to help patients with ocular muscle palsies. In a large series of cases Lyle and Cross in 1951[1] showed that these patients can be assisted greatly by operation. It is the purpose of this article to emphasize that in congenital and traumatic extra-ocular muscle palsies the results of suitable operative measures are excellent.

CONGENITAL OCULAR MUSCLE PALSIES

A few cases are hereditary; some are due to developmental defects of muscles or cranial nuclei and others to birth injury. They are seldom recognized during the first year of life and are commonly overlooked until childhood or even adult life. Minimal ocular palsies may cause considerable eye strain yet be dismissed as a minor muscle imbalance or be treated by orthoptic exercises.

Children may develop an extraordinary degree of vertical movement of the eyes in order to maintain single binocular vision. No serious symptoms may be experienced during childhood or early adult life, but about middle life the muscular compensation may break down and lead to double vision. Prisms are often prescribed in spectacles to relieve heterophoria or double vision, and the underlying ocular muscle palsy is unrecognized. Sometimes direct questioning elicits the information that double vision is experienced during fatigue, and the habit may be formed of closing one eye in certain directions of gaze to avoid double vision.

In more severe palsies the effort to retain binocular vision gives rise to head-tilting. Should a head tilt or ocular torticollis persist during childhood and puberty, the face may develop asymmetry. The sternomastoid muscle is occasionally operated upon in an attempt to cure the torticollis; this, of course, is ineffective because the head is tilted in order to maintain single vision. One such case occurred in this series (M.H.). A palsy that is too severe to permit compensation leads to a squint and the squinting eye usually becomes amblyopic.

Acquired ocular muscle palsies.—Sudden onset of double vision is such a handicap that patients quickly seek advice. The patient complains of vertigo, giddiness, and confusion in traffic, and that he finds it necessary to close or cover one eye. These patients should be questioned carefully to ascertain whether the images are one above the other, or side by side. Vertical diplopia means that the vertically acting muscles

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are involved. Horizontal diplopia implicates the horizontally acting recti.

Diagnosis of muscle affected.—One of the most valuable tests is the cover test. This consists of two parts: (1) The patient looks at a distant light and one eye is covered by the examiner. If the eye moves to look at the light on being uncovered, a muscle anomaly is present. (2) With the patient looking at the distant light, the examiner covers one eye and then the other alternately. If on moving the cover from one eye to the other, the eye makes a slight movement in order to renew fixation, then there is some muscular imbalance.

Slight degrees of paresis may be missed if the patient is merely asked to look up and down, to the right and to the left, because diplopia may occur only at, or near, the limit of rotation in the appropriate diagnostic direction of gaze.

In doubtful cases the test may be made more accurate by using goggles with red filter before the right eye, and a green filter before the left eye. The patient then looks at a light which is moved in the directions of gaze. The direction in which separation between the red and green lights is maximal is readily determined. The image which is most displaced belongs to the affected eye. The Hess and Lancaster screen tests

DIAGRAM TO SHOW THE 6 DIAGNOSTIC DIRECTIONS OF GAZE

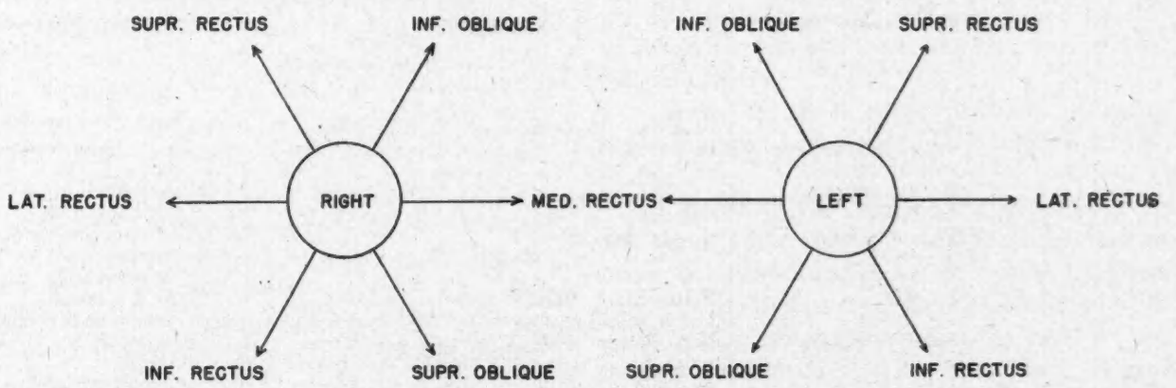

Fig. 1

Fig. 1 is a simple diagram showing the direction in which each eye muscle has its maximum effect. With this diagram in mind it is easy to decide which muscle is paralysed, unless more than one is affected.

If the paralysis is severe, limitation of movement will be obvious in the direction in which the affected muscle acts maximally. Slight paralyses are less obvious, but can be recognized by the following test. First, determine the direction in which the double images are most widely separated. This will limit the paralysis to one muscle in each eye. For example, if the diplopia is maximal up and to the right, then either the right superior rectus or the left inferior oblique is at fault. Then cover and uncover one eye to determine to which eye the most displaced image belongs. In the example, if the upper image belongs to the right eye, then the right superior rectus is the paralysed muscle.

are still more accurate, but the diagnosis may be made without them.

Investigation of cause.—It is not intended to give a full account of investigations needed to determine the cause of a palsy. The most important single investigation is the taking of a careful history. The history of a blow on the head preceding the development of diplopia suggests a traumatic origin, and sudden onset in an elderly person suggests a vascular cause. A gradual onset, at any age, is suggestive of a cerebral tumour.

Many investigations may need to be carried out. A general examination is necessary to exclude such systemic causes as disseminated sclerosis, and the urine and blood should be examined to exclude diabetes. Hypertension in the elderly is a common accompaniment of a vascular diplopia. The ocular fundi must be examined for papilloedema, and the visual fields checked to exclude an intracranial lesion.

TABLE I.

Case	*Age*	*Sex*	*Muscle affected*	*Etiology*	*Treatment*	*Result*
J.C.M.	72	M.	Lt. L.R.	Vascular	None	Recovery in 4 months.
L.E.H.	47	F.	Lt. S.O.	Congenital	Refused operation	No change. Occasional diplopia. 8△ Lt. hyperphoria.
F.C.P.	58	M.	Rt. I.O.	Vascular	None	Recovery in 10 days.
E.G.	20	F.	Lt. S.R.	Trauma	None	Recovery in 6 weeks. 3△ residual Rt. hyperphoria.
L.M.	12	M.	Rt. S.O. 20△ esotropia 14△ Rt. hypertropia	Congenital	1st operation: Rt. I.O. myectomy. and Rt. M.R. recession. 2nd operation: Rt. S.R. recession and Lt. L.R. resection.	No binocular vision. Rt. 20/15: Lt. 20/30. 6△ esotropia 3△ Rt. hypertropia. Cosmetically straight.
H.W.	43	M.	Lt. S.R.	Congenital	Refused operation	Occasional diplopia. 12△ to 20△ Rt. hyperphoria.
S.D.	65	M.	Lt. L.R.	Vascular	None	Recovery in 3 weeks.
E.C.	45	F.	Lt. L.R.	Disseminated sclerosis	None	Recovery in 10 days.
E.C.	21	M.	Rt. S.R. 16△ exophoria 27△ to 44△ Lt. hyperphoria	Congenital	1st operation: Rt. I.R. recession and Lt. O.I. myectomy. 2nd operation: Lt. S.R. recession. and Lt. L.R. recession.	Rt. 20/40: Lt. 20/15. 2nd grade binocular vision. 4△ exophoria. 4△ Lt. hyperphoria.
D.G.	48	F.	Lt. S.R. 4△ exophoria 25△ to 30△ Rt. hyperphoria	Followed extraction of 14 teeth at one time.	Rt. I.O. myectomy and Lt. I.R. recession.	Rt. 20/20: Lt. 20/20. 3rd grade binocular vision. 2△ exophoria 3△ Rt. hyperphoria.
E.F.	52	M.	Lt. S.R. 10△ esophoria 9△ to 11△ Lt. hyperphoria	Trauma	Rt. I.O. myectomy.	Rt. 20/30: Lt. 20/20. 3rd grade binocular vision. 4△ esophoria 1△ Lt. hyperphoria.
K.F.	32	F.	Lt. S.O. 4△ to 7△ Lt. hyperphoria	Followed 3 fillings and 3 dental extractions at one sitting.	Marginal myotomy Rt. I.R. under local anæsthesia with Maddox rod control.	Rt. 20/20: Lt. 20/20. 3rd grade binocular vision Lt. hyperphoria 2△. No symptoms.
E.W.	58	M.	Lt. S.R.	Vascular	None	Recovery in 3 weeks.
D.T.	23	F.	Rt. S.R.	Disseminated sclerosis.	None	Recovery in 10 days.
A.M.	25	M.	Rr. S.R. 6△ to 10△ Lt. hyperphoria	Congenital	Lt. I.O. myectomy	Rt. 20/15: Lt. 20/15. 3rd grade binocular vision. 2△ exophoria 2△ Lt. hyperphoria.
C.W.	73	F.	Lt. S.R.	Vascular	None	Recovery in 2 weeks.
W.S.	56	M.	Rt. L.R. 24△ to 30△ esotropia.	Trauma	Lt. M.R. recession.	Rt. 20/20: Lt. 20/20. 3rd grade binocular vision. 10△ esophoria. A further operation was suggested to reduce this muscular imbalance but patient felt he was already cured since he had no diplopia.
B.D.H.	17	F.	Rt. S.R. and rt. I.O.	Congenital	Recession Lt. S.R. and resection Lt. I.R.	Rt. 20/30: Lt. 20/30. No binocular vision. Cosmetically straight.
C.E.E.	46	M.	Lt. S.R. 7△ to 8△ Rt. hyperphoria 2△ esophoria.	Congenital	Rt. I.O. myectomy.	Rt. 20/20: Lt. 20/20. 3rd grade binocular vision. 1△ Rt. hyperphoria.
S.C.	62	M.	Rt. L.R.	Vascular	None	Recovery in 4 weeks.
G.R.	22	M.	Rt. S.R.	Trauma	None	Recovery in 7 days.
S.Y.	32	M.	Lt. L.R. 20△ esotropia.	Trauma	Rt. M.R. recession.	Rt. 20/30: Lt. 20/20. 3rd grade binocular vision. 2△ esophoria.
S.H.	13	F.	Rt. L.R. and lt. L.R.	Astrocytoma of cerebellum.	Operation by neurosurgeon.	Reported to be straight. Not seen after operation.
J.S.	15	M.	Rt. I.R. 7△ to 14△ Rt. hyperphoria 4△ exophoria	Trauma	Rt. S.R. recession.	Orthophoria. 3rd grade binocular vision.

TABLE I.

Case	*Age*	*Sex*	*Muscle affected*	*Etiology*	*Treatment*	*Result*
M.H.	12	F.	Rt. I.R. 12△ Rt. hypertropia. 14△ esotropia.	Congenital	1st operation: Rt. S.R. recession. 2nd operation: Rt. I.R. resection.	Rt. 20/40: Lt. 20/20. 2nd grade binocular vision. 4△ esophoria. Had previously had operation on sternomastoid for head tilt.

I—inferior
L—lateral
M—medial
O—oblique
R—rectus

S—superior
Rt.—right
Lt.—left

△—prism dioptres.

MANAGEMENT

These patients often require the combined attention of the ophthalmologist and another specialist. Those cases due to disseminated sclerosis or a vascular lesion almost always recover without any ophthalmic treatment. It is the congenital and traumatic cases for which the eye surgeon can do most. In congenital cases in which no binocular vision is present and the patient is over the age of 8 when seen, surgery is unlikely to cause binocular vision to develop, but the eyes may be made cosmetically straight and the patient thereby relieved of the psychological burden of an unsightly deformity.

The traumatic cases improve up to a period of four months or even one year as the muscle and its associated nerve recover. During this time the patient should be seen at intervals of three weeks to record the degree of muscular imbalance with the Maddox rod and Hess screen tests. These findings give an accurate assessment of the rate of recovery. When on two successive visits the findings are the same, indicating that improvement is not being maintained, operation should be advised. This usually occurs after about six months.

During this period of recovery the patient is greatly relieved if correcting prisms are incorporated in the spectacles to permit single binocular vision. A partial correction is advisable so as to leave a constant stimulus to recovery.

Surgical measures.—Paralysis of an extra-ocular muscle leads to contraction of the antagonist of the same eye, and in the other eye to overaction of the synergist and inhibitional palsy of the antagonist. An overacting or contracted muscle is weakened by moving its insertion nearer to its origin, and an underacting muscle is strengthened by shortening it or advancing its insertion. Patients should be warned that two or three operations are sometimes required to correct the muscle imbalance.

Small degrees of paralysis may be relieved by operating under local anæsthesia and using a Maddox rod and light as a control. This method gives very good results, and one patient in this series (KF) who was treated in this way became orthophoric.

A series of 25 cases of paralysis of extra-ocular muscles is reported in the following table (Table I).

The girl with the astrocytoma of cerebellum was admitted to the eye ward for operation as a case of intermittent convergent squint. It was only during the preoperative examination that slight papillœdema was observed and it was realized that an intracranial lesion was present.

The two patients who developed the palsy after teeth extractions both regained full binocular vision after operation, although one (DG) required a prismatic correction in her spectacles to correct a small residual heterophoria.

Eight cases were congenital and six were traumatic in origin. The results in those patients submitted to operation were uniformly good. Not all of the patients with congenital palsies obtained full binocular vision, but all ended with eyes cosmetically straight. The six with traumatic palsy all regained full binocular vision.

SUMMARY

Congenital ocular muscle palsies are often overlooked, and occur more frequently than is generally realized. The results of surgery in congenital and traumatic cases are excellent. A series of 25 cases of extra-ocular muscle palsy is reported.

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ELECTROCARDIOGRAMS IN THE PERIODIC HEALTH EXAMINATION OF EXECUTIVES AND SUPERVISORS*

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SINCE 1949, annual electrocardiograms have been made available to selected employees of a large industrial organization. With few exceptions, the examinations, which form part of the company's general health program, have been restricted to male and female employees, age 40 and over, occupying executive or supervisory positions.

The application of electrocardiography to the field of industrial medicine is becoming increasingly common. Through clinical experience, supported by both physiological and pathological evidence, electrocardiography has become a recognized diagnostic aid where heart disease is suspected. Less is known of its value as a screening test of apparently healthy people. The rationale for including an electrocardiogram as part of the periodic health examination is based upon the belief that it will assist the examining physician to reach a more accurate assessment of the health of the employee than would be possible to achieve without it. In those with symptoms and signs of heart disease, it may provide confirmatory evidence or permit a more accurate definition of the ailment; notably will this apply where the clinical findings are equivocal. A normal electrocardiogram, on the other hand, in a presumably healthy person, particularly if he is over the age of 40, will add weight to a favourable opinion expressed by the attending physician.

The apparently healthy person whose electrocardiogram gives the first indication of underlying heart disease presents a perplexing problem. Does the abnormal electrocardiogram found under these circumstances necessarily have the same clinical connotation as it does when associated with some recognized form of heart disease? Are changes in heart muscle sufficient only to produce non-specific alterations in the electrocardiogram necessarily progressive and may they not be compatible with years of useful employment and freedom from functional disability? It was apparent from the beginning that a partial answer to these questions lay in following up, for a period of years, those who entered the study and measuring the progress of their health by periodic re-examination.

It is the purpose of this report to present the results of an analysis of data pertaining to those examined between the years 1949 to 1952. The frequency of abnormal electrocardiograms has been calculated from the cumulative figure for those examined for the first time during the study period. Insufficient follow-up experience as yet precludes any reliable conclusions concerning the significance of the observed abnormalities. However, selected case reports give some indication of the effectiveness of the programme.

PROCEDURE

The electrocardiograms were taken by physicians and institutions in various parts of Canada. For the purpose of uniformity, it was laid down in 1949 that electrocardiograms were to consist of the three standard limb leads and the four precordial leads, CF 2, 3, 4 and 5. A standardization deflection was to be incorporated in each lead. In subsequent years there was considerable variation in the leads submitted. With the wider acceptance of the Wilson indifferent electrode, the majority of precordial leads are now of this type. The use of different reference electrodes in serial tracings of an employee did not interfere with the interpretation as long as the leads were clearly identified.

The electrocardiograms were forwarded to this laboratory through the office of the Medical Director of the company. With each was a card containing a summary of current clinical findings. The interpretations were returned to the office of the Medical Director and at the end of the year photostatic copies of all electrocardiograms were prepared in duplicate, one copy for retention in the office of the Medical Director and the other to be forwarded to the medical officer of the plant where the employee worked.

RESULTS

General.—The number of initial examinations and the number of re-examinations for the years 1949, 1950, 1951 and 1952 are shown in Table I.

TABLE I.

NUMBER OF EXAMINATIONS BY YEARS

Year	First examination	Re-examination		
		1950	*1951*	*1952*
1949	221	151	24	95
1950	47	—	2	16
1951	14	—	—	10
1952	80	—	—	—
Total	362	151	26	121

Between 1949 and 1952, 362 different employees had their first electrocardiogram in connection with the survey. There was a wide variation each

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year in the number taking advantage of the opportunity to be re-examined. This was due in part to the fact that examinations were necessarily on a voluntary basis and also to such uncontrollable factors as "retired because of age", "no longer eligible", "transferred to the United States" and "sought other employment". Of the 221 examined initially in 1949, only 95 presented themselves for re-examination in 1952 (Table I).

GENERAL AND ELECTROCARDIOGRAPHIC CHARACTERISTICS OF 362 EMPLOYEES AT THE TIME OF THEIR INITIAL EXAMINATION

1. *Age and sex.*The distribution of the population by age and sex is shown in Table II.

TABLE II.

DISTRIBUTION OF POPULATION BY AGE AND SEX

	Sex				
	male		female		
Age groups	*number*	*percent*	*number*	*percent*	*Total*
20 - 39	49	98	1	2	50
40 - 49	157	87	23	13	180
50 - 59	87	84	16	16	103
60+	29	100	0	—	29
Total.....	322	89	40	11	362

2. *Cardiovascular classification.*—Based upon the results of the annual health examinations, employees were placed in one of three categories, according to the probability of their having cardiovascular disease. The first group, *normal,* had no evidence of heart disease. In such people there would be no reason on purely clinical grounds for requesting an electrocardiogram. The second group, *questionable,* had no positive evidence of heart disease but the possibility could not be excluded. This group included those with moderate hypertension* (14%†); overweight in excess of 25% of standard weight for height (7%†); diabetes mellitus; history of rheumatic fever; heart murmurs and history of chest pain not clearly due to heart disease. The third group, *abnormal,* had a definite history of myocardial infarction; angina pectoris; marked hypertension* (7%†); organic heart murmurs; etc. The age distribution according to this classification is presented in Table III.

TABLE III.

CARDIOVASCULAR CLASSIFICATION

Age groups	*Normal*		*Questionable*		*Abnormal*		*Total*
	No.	*%*	*No.*	*%*	*No.*	*%*	
20 - 39	40	80	8	16	2	4	50
40 - 49	133	74	43	24	4	2	180
50 - 59	58	56	24	23	21	21	103
60+	17	59	8	27	4	14	29
Total.....	248	68	83	23	31	9	362

3. *Electrocardiographic classification.* – The electrocardiograms were arranged also in three classes according to the normality of the form of the record: normal, questionable, and abnormal. This classification was adopted because of uncertainty concerning the significance in apparently healthy persons of certain electrocardiographic configurations which are commonly accepted as confirmatory evidence of specific disturbances in the heart. The abnormal group included marked displacement of RS-T segments, low diphasic or inverted T1 or T2, low voltage T waves, Q1T1 and Q3T3 patterns, right or left bundle branch block and right or left ventricular hypertrophy patterns. It would have included also gross disturbances in rhythm and conduction but none of these were encountered. Minor conduction defects, premature beats from two or more foci, isolated abnormal QRS-T components and minor differences in configuration from year to year were classified as questionable. The age distribution of the population according to this classification of electrocardiograms is shown in Table IV.

TABLE IV.

E.C.G. CLASSIFICATION

Age groups	*Normal*		*Questionable*		*Abnormal*		*Total*
	No.	*%*	*No.*	*%*	*No.*	*%*	
20 - 39	39	78	9	18	2	4	50
40 - 49	135	75	38	21	7	4	180
50 - 59	73	71	22	21	8	8	103
60+	17	59	7	24	5	17	29
Total.....	264	73	76	21	22	6	362

4. *Relationship between cardiovascular and electrocardiographic classification.* – Some indication of the value of electrocardiography as a

*Moderate hypertension: > 140 mm. Hg. systolic and/or 90 mm. Hg. diastolic.
Marked hypertension: > 160 mm. Hg. systolic and/or 100 mm. Hg. diastolic.
†Of total population.

primary selection screen for populations of this age and occupation may be obtained by examining the relationship of the cardiovascular health of these people to the normality of their electrocardiograms. The data are presented in Table V. Of the 248 employees who showed no evidence of cardiovascular disease, 19% had electrocardiograms exhibiting some degree of abnormality. In the cardiovascular "questionable" group, the figure was 40%, while in those with established heart disease it was 55%. As the probability of cardiovascular disease increased, so did the frequency of abnormal electrocardiographic findings. The relationship is statistically significant ($P < 0.01$).

TABLE V.

RELATION OF CARDIOVASCULAR TO E.C.G. CLASSIFICATION

Cardiovascular classification	*E.C.G. classification*						*Total*	
	Normal		*Questionable*		*Abnormal*			
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Normal.....	200	81	37	15	11	4	248	68
Questionable..	50	60	29	35	4	5	83	23
Abnormal....	14	45	10	32	7	23	31	9
Total....	264	73	76	21	22	6	362	100

Whereas one might expect to find abnormal electrocardiograms in persons with recognized heart disease, it is noteworthy that in the cardiovascular "normal" group 4% of the electrocardiograms were definitely abnormal. In a similar study, Wood, Wolferth, and Miller[1] also observed abnormal electrocardiograms in 4% of apparently healthy people. Only by observing such people for a period of years, can the clinical significance of their abnormal electrocardiograms be established.

95 Persons Examined in 1949 and Followed Through to 1952

Difficulties experienced in obtaining follow-up data on those previously examined have already been pointed out. The electrocardiographic findings on the 95 persons examined both in 1949 and 1952 are shown in Table VI.

Of the 69 persons whose original electrocardiograms were normal, 80% were still normal in 1952; 16% became questionable and 4% grossly abnormal. Of the 23 individuals with questionable electrocardiograms in 1949, 39% returned to normal, 35% remained questionable and 26% progressed to definite abnormality. Faulty recording technique accounted for 5 of the 9 questionable records that subsequently returned to normal. It is noteworthy that a higher percentage of questionable electrocardiograms progressed to definite abnormality (26%) than in the group originally classified as normal (4%). The three employees whose electrocardiograms were abnormal in 1949 continued to show similar abnormal records in 1952.

TABLE VI.

E.C.G. CLASSIFICATION OF PERSONS EXAMINED IN 1949 AND 1952

1949			*1952*					
			Normal		*Questionable*		*Abnormal*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Normal.....	69	73	55	80	11	16	3	4
Questionable..	23	24	9	39	8	35	6	26
Abnormal....	3	3	—	—	—	—	3	100
Total....	95	100	64	67	19	20	12	13

Case Histories

While the limited size of the population and the relatively short follow-up period prevent a statistical evaluation of the significance of the abnormal electrocardiograms, the following case reports give some indication of the experience to date.

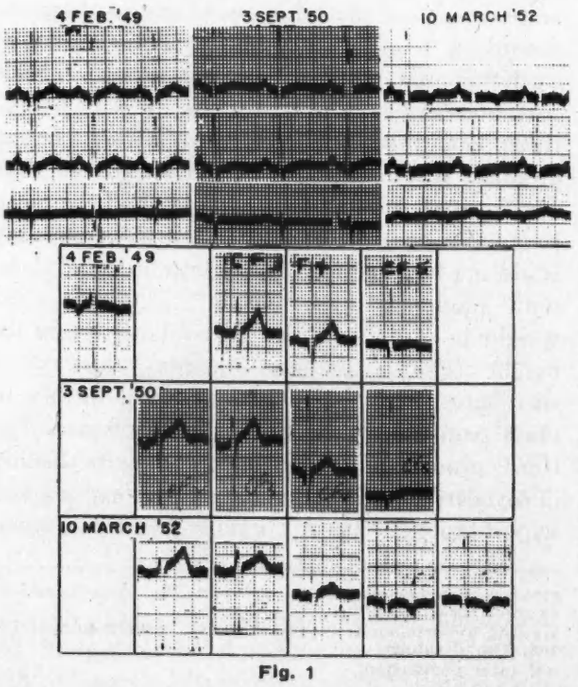

Fig. 1

CASE 1 (No. 55): This employee, aged 59, was examined initially on February 4, 1949. Apart from vague joint pains, he was asymptomatic and there were no significant past illnesses. Physical examination was negative except for hypertension. Ht. 59″; wt. 195 lb.; B.P. 175/100. On September 3, 1950, his blood pressure was 200/110 and on March 10, 1952, it was 180/100. His electrocardiograms are shown in Fig. 1.

The electrocardiogram of February 4, 1949, was interpreted as normal, although the combined amplitudes of S_{CF1} and R_{CF4} equalled 37 mm. Nineteen months later (September 3, 1950), the T voltage in the standard limb leads had fallen, as had T_{CF5}. By March 10, 1952, RS-T1&2 were depressed, T1&2 were inverted, RS-T_{CF6} was depressed and $T_{CF5\&6}$ were inverted.

During the period of observation, this man remained fully occupied and asymptomatic in spite of a persistently elevated blood pressure. The serial electrocardiograms showed progressive changes indicating hypertrophy of the left ventricle.

Here the electrocardiogram assisted in documenting the course of the disease and warned the physician of a change in the patient's clinical state, which was not otherwise detectable.

CASE 2 (No. 83): On February 24, 1949, this 53 year old man was asymptomatic and there were no significant findings on examination. Ht. 68″; wt. 162 lb.; B.P. 110/70. He was re-examined on June 26, 1950 with similar results. On June 20, 1951, there were still no positive findings but it was reported that his gastrointestinal tract had been investigated because of recent indigestion. He developed an acute myocardial infarction on December 26, 1951. He returned to work subsequently and was last examined on September 16, 1952. He now suffers from angina pectoris on exertion or when emotionally disturbed. His electrocardiograms are shown in Fig. 2.

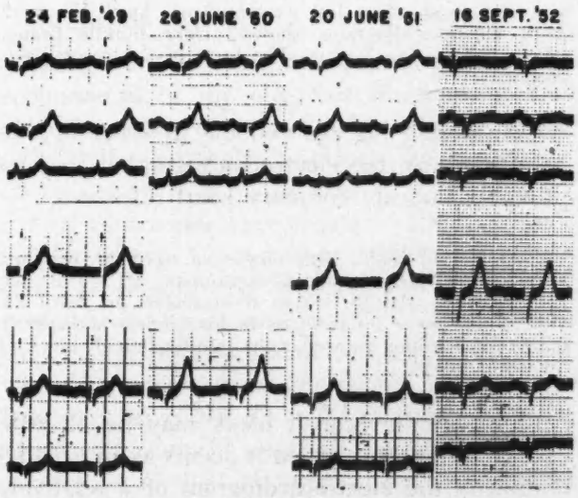

Fig. 2

The tracings recorded in 1949, 1950 and 1951 were each read as normal. Within 6 months of the 1951 record, he had a classical acute myocardial infarction. The 1952 record shows the end result of this episode.

A series of 3 electrocardiograms, taken a year apart, the most recent within approximately 6 months of an acute myocardial infarction, failed to give any indication of the events which followed.

CASE 3 (No. 123): This 49 year old male was first examined on March 26, 1949. He was asymptomatic and there were no positive physical findings with the exception of varicose veins. Ht. 69½″; wt. 152 lb.; B.P. 116/54. He was re-examined on September 13, 1950, and again on April 8, 1952. No change in his clinical condition was reported except for an increase in weight to 180 lb. The electrocardiograms recorded at the time of his clinical examinations are shown in Fig. 3.

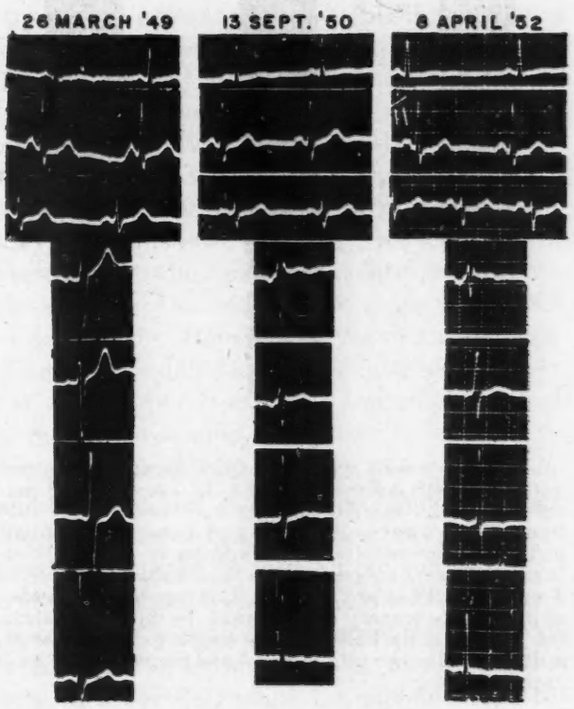

Fig. 3

In the 1949 tracing, T3 is tall, while T1 is low and tends to be inverted, although electrically the heart is not vertical. The RS-T segments in CF4&5 are slightly depressed. In the record of 1950, the precordial T wave voltage is lower than previously recorded, and the limb lead T wave changes are still present. Further deterioration in the precordial T waves is seen in the 1952 tracing, $T_{CF4\&5}$ now being inverted. The $T1 < T3$ relationship is still present in the limb leads.

This employee's electrocardiogram was abnormal when he was first seen and over the following years progressive changes took place suggesting coronary heart disease. Throughout the observation period, he apparently remained asymptomatic.

CASE 4 (No. 128): This employee, aged 61, was examined on March 26, 1949. He felt well and there were no significant findings on examination. Ht. 66″; wt. 158 lb.; B.P. 112/64. He was next examined on September 7, 1950. There were no important clinical findings apart from a recent attack of renal colic. He was last seen on

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April 8, 1952, at which time he had no complaints. B.P. 150/88. Electrocardiograms taken in conjunction with the clinical examinations are shown in Fig. 4.

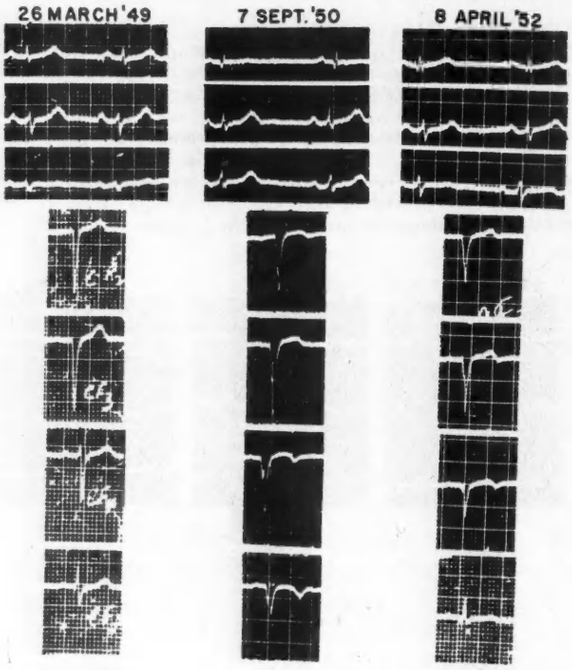

Fig. 4

The 1949 record shows low QRS voltage in the limb leads and a QS deflection in CF3. It was otherwise considered normal. Definite changes were noted in the 1950 tracing. A Q wave is present in lead 1 and the amplitude of T1 has fallen with reciprocal increase in T3. QS deflections or Q waves are present in all precordial leads and the T waves in CF4&5 are inverted. This record was classified as indicating coronary heart disease. In the 1952 tracing, the T waves in the limb leads are similar to those observed in 1949, but the Q waves in lead 1 and the precordial leads have persisted.

Although this employee remains asymptomatic, the electrocardiographic picture strongly suggests coronary heart disease with the distinct possibility of there having been a silent or unrecognized myocardial infarction some time between March 26, 1949 and September 7, 1950.

CASE 5 (No. 146): This employee, aged 60, was first examined May 30, 1949. Apart from a history of duodenal ulcer, he was asymptomatic and general examination was essentially negative. Ht. 67″; wt. 150 lb.; B.P. 150/88. He was re-examined on November 27, 1950 and again on April 8, 1952. On neither occasion were there positive clinical findings. He died suddenly on November 12, 1952, seven months after his last examination. The clinical diagnosis was acute myocardial infarction. There was no autopsy. His electrocardiograms are shown in Fig. 5.

The records of 1949 and 1950 were both read as normal although, in the 1950 record, T1 was minimally lower than the year before. The 1952 record was classified as questionable because of the fall in T wave voltage and particularly the flat T1. Greater emphasis would have been placed upon these findings had the heart not been vertically placed, a factor which favours small values in all components of lead 1.

In this case, electrocardiographic signs of coronary heart disease were present at least seven months before this man died of what was presumably an acute myocardial infarction.

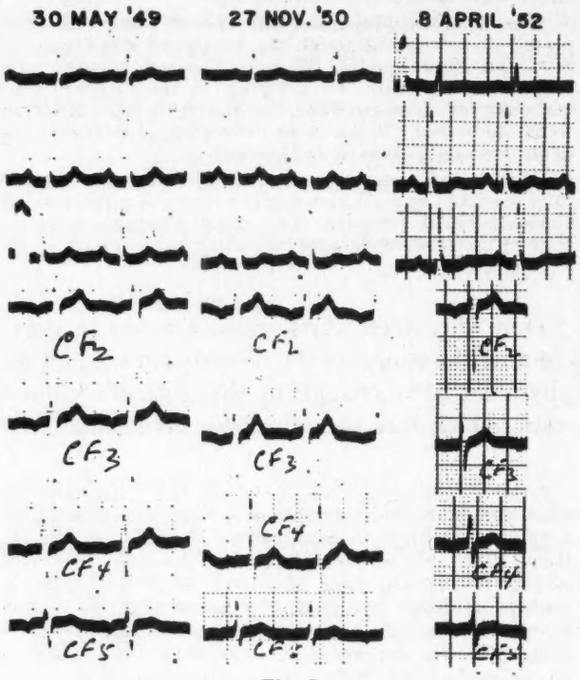

Fig. 5

CASE 6 (No. 31): This 61 year old diabetic was examined on January 11, 1949. He felt well and there were no symptoms referable to the cardiovascular system. Ht. 68″; wt. 193 lb.; B.P. 158/88. His clinical status was the same when last examined on April 17, 1952. Both electrocardiograms showed right bundle branch block of the wide S type. The form of the records was constant.

Considering his age and the presence of diabetes mellitus, the electrocardiographic changes probably indicate coronary heart disease.

CASE 7 (No. 243): This employee, aged 39, was first examined in 1950. He was asymptomatic. Ht. 74½″; wt. 210 lb.; B.P. 118/78. When re-examined on April 24, 1952, there were no changes in his clinical state. Both electrocardiograms showed right bundle branch block of the wide S type.

Right bundle branch block may be of little clinical significance when it occurs as an isolated finding in the electrocardiogram of a relatively young person who is otherwise in good health. Recognition of this fact by the attending physician is essential in assessing the clinical status of persons so affected.

CASE 8 (No. 153): This employee, aged 49, was first examined on June 3, 1949. There were no symptoms and no positive findings on examination. Ht. 65″; wt. 149 lb.; B.P. 135/75. He was re-examined on November 23, 1950

and again on April 25, 1952. There were no changes in his clinical condition. His electrocardiograms appear in Fig. 6.

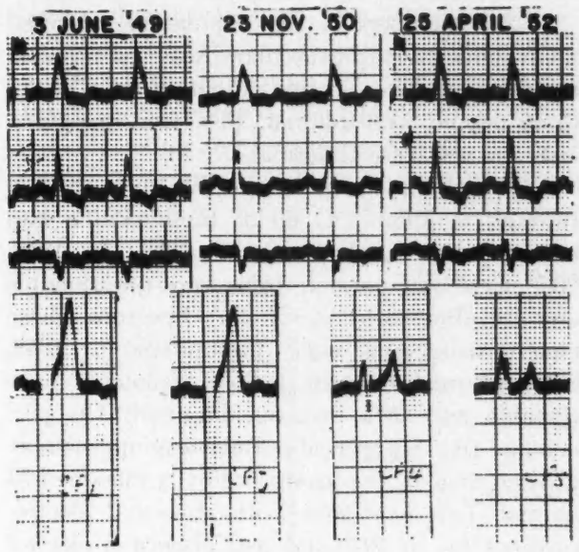

Fig. 6

Left bundle branch block is seen in all records and the form is fundamentally constant.

Left bundle branch block is more likely to be due to heart disease than right bundle branch block, but its presence should not be overstressed in a person who otherwise maintains good health. It may be compatible with many years of useful employment.

DISCUSSION

While various types of abnormality may be encountered in the electrocardiograms of employed persons re-examined periodically, those seen will commonly fall into one of three classes:

Left ventricular hypertrophy. – Electrocardiographic changes indicative of left ventricular strain or hypertrophy will be found usually in persons who are known on clinical grounds to have one of the conditions commonly associated with left ventricular hypertrophy, particularly hypertension (Case 1) or aortic valvular heart disease. Here serial electrocardiography may be a sensitive method of indicating increasing left ventricular hypertrophy.

Coronary heart disease. – Changes in the QRS-T components will seldom present the picture of acute myocardial infarction. More commonly, significant Q waves, low QRS voltage and T wave changes without associated RS-T segment shift will be encountered. While such changes are due usually to chronic coronary heart disease, other causes have to be excluded. The clinical picture here is of first importance. If there are no symptoms, the probability of coronary heart disease is increased if the observed changes are progressive in serial records (Cases 3 and 4). Care must be taken to exclude the progressively diminishing voltage of myxœdema. Left ventricular hypertrophy is unlikely to cause confusion if there is no clinical reason to support its presence. In reversible myocardial ischæmia associated with coronary heart disease it is not uncommon to find fluctuating reciprocal variations in the relative amplitudes of T1 and T3 (Cases 4 and 5). Apart from intraventricular conduction defects, there are abnormal QRS configurations which remain constant throughout the years. Such changes may represent the end result of myocardial damage secondary to coronary heart disease, but may reflect also the presence of a thickened or calcified pericardium, the sequela of an unidentified acute pericarditis in earlier life. Here also myxœdema and congenital anomalies have to be excluded. Where the abnormality is fixed the immediate outlook is usually favourable.

Bundle branch block. – Of the fixed abnormalities that are encountered, bundle branch block requires special mention. Occasionally it may be transient or intermittent but is usually constant. Bundle branch block is known to occur in conjunction with intraventricular septal defects, and it is not unreasonable to suppose that even in lesser degrees of incomplete union the conduction pathways may be interrupted. Apart from congenital anomalies, the microscopic size of the bundles make them particularly susceptible to interruption by small lesions which may occur without necessarily causing gross damage to the heart. Various electrocardiographic studies[2 to 6] of healthy persons include instances of bundle branch block. It is the right bundle branch which is the more commonly affected.

Left bundle branch block occurs less frequently. It is seen usually in the electrocardiograms of older people, and is more likely to be associated with myocardial disease. When it is present in an otherwise healthy person, even left bundle branch block may be compatible with may years of active life.

Having emphasized the favourable outlook which may be associated with bundle branch block, it is also important to recognize that both types may occur in association with serious heart

disease, particularly coronary heart disease. The differentiation rests upon the clinical assessment of the individual, favourable prognosis being stressed in younger people who fail to show other evidence of disease.

Many abnormal electrocardiograms lack specificity. In such instances where there is no reasonable evidence to suggest a clinical connotation it is proper to state that the cause of the abnormality is unknown. This practice at least avoids misleading the attending physician.

The results of this study suggest that the electrocardiogram is a useful adjunct to the periodic health examination. It forms a permanent record for future reference should the problem of heart disease arise. In selected cases it serves to document the course of progressive disturbances in the myocardium. It may identify coronary heart disease when it is otherwise not detectable. Like other useful procedures it has important limitations. Serious coronary heart disease may exist with a normal electrocardiogram, and all abnormal electrocardiograms are not necessarily indicative of serious heart disease. The significance of the observed changes rests primarily upon the associated clinical findings. Asymptomatic persons with abnormal tracings may enjoy many years of useful employment without limitation of function. Without doubt such people belong to a group that will experience a greater than normal incidence of cardiovascular disability, but the electrocardiogram by itself is a poor means of predicting the immediate future health of an asymptomatic person.

SUMMARY AND CONCLUSIONS

1. Electrocardiograms were recorded on 362 persons, aged 40 and over, occupying executive or supervisory positions in industry; 73% of the tracings were normal in form, 21% were questionable, and 6% were abnormal.

2. 248 members of the population exhibited no evidence of cardiovascular disease on physical examination. The electrocardiograms of 81% of these people were normal, 15% were questionable and 4% were abnormal.

3. 95 individuals were followed up from 1949 through to 1952: (a) 69 of these people had normal electrocardiograms in 1949. In 1952, 80% were still normal; 16% were questionable and 4% abnormal. (b) Of the 23 persons whose electrocardiograms were questionable in 1949, 39% returned to normal, 35% remained questionable and 26% became abnormal. The percentage that became abnormal was appreciably greater than in the group orginally classified as normal. (c) 3 persons with abnormal electrocardiograms in 1949 still had abnormal electrocardiograms in 1952.

4. Illustrative cases are presented to show the types of electrocardiographic abnormalities which were observed during the study.

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HAZARDS IN THE USE OF ANTIBIOTICS*

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ANTIBIOTIC THERAPY is no longer a simple matter. The doctor in his choice of an antibiotic now must accept a calculated risk in terms of the benefit which may accrue to the patient and toxic sequelæ which may develop. The indiscriminate use of a relatively non-toxic drug, such as penicillin, is no longer to be condoned. In his selection of an antibiotic the physician must take into account the possibility that the condition may be caused by an organism not susceptible to the antibiotic. Further, there is the inherent risk of drug toxicity and the possibility that a sensitivity reaction may occur, or more pertinent, that the patient may be sensitized so that he will be denied the benefits of the antibiotic at a later date.

With respect to the question of bacterial sensitivity and drug resistance, a knowledge of the

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site of action of common antibiotics is helpful.

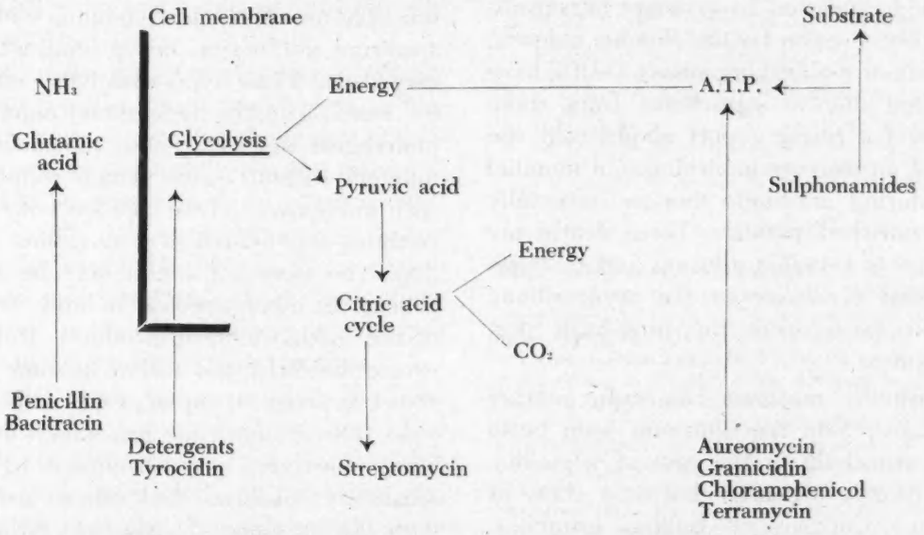
Penicillin prevents the uptake of glutamic acid, the lack of which is more important to bacteria than to the host. This also accounts for the lag in the action of penicillin. Streptomycin interferes with metabolism in the citric acid cycle for susceptible bacteria. Many organisms circumvent this action and become resistant.

Broad spectrum antibiotics, such as aureomycin, terramycin and chloramphenicol (Chloromycetin) interfere with the synthesis of adenosine triphosphate, which is one of the energy-producing materials used in the synthesis of more complex cellular components. The action of these substances is consequently broader than penicillin. Sulphonamides act by blocking enzymatic actions with respect to the growth of bacteria and use of substrate materials. Para-aminobenzoic acid is the basic substance related to sulphonamide activity.

In order to obtain a killing effect, the concentration of antibiotics in the tissues must be several times higher than that needed for bacteriostatic effect. For example, some organisms such as the gonococcus and hæmolytic streptococcus are extremely susceptible to penicillin, but most of the effects in average dosage are probably bacteriostatic. Further, the defences of the host must play a significant part and this is especially so in the disposal of micro-organisms which have been damaged by the antibiotic.

The natural and acquired resistance of the micro-organism is also important. When penicillin was first introduced most strains of staphylococci were susceptible. The resistant strains may naturally have the ability to elaborate penicillinase which inactivates penicillin, or new strains may develop. As mentioned before, penicillin inhibits the assimilation of glutamic acid and as new resistant strains arise they appear to lose their ability to take up glutamic acid, but gain the property of synthesizing their needed amino acids, eventually requiring only ammonia and glucose for this purpose.

SITE OF ANTIBACTERIAL ACTION



Some feel that penicillin does not induce mutation, but by holding down the growth or by eliminating the sensitive organism it permits the growth of resistant variants. A recent survey shows that in the area studied 60% of strains of hæmolytic *Staphylococcus aureus* were resistant to penicillin, 25% resistant to aureomycin and terramycin, and 17% resistant to chloramphenicol. Recurrent furuncles due to staphylococci, resistant to all the common antibiotics, are now appearing. It is well to remember that an autogenous vaccine may be life-saving in these cases.

In the case of streptomycin, resistance develops quickly in one to five days. Bacterial mutants actually incorporate the streptomycin into their metabolic cycle. Because of this, the use of penicillin-streptomycin combinations should not be continued over a long period of time. Coliform organisms are prone to develop resistance quickly and this is of some concern in the treatment of urinary infections.

Resistance in the case of the broad spectrum antibiotics develops slowly and in a step-like

fashion. It may increase two to four times, but strongly resistant, fast or dependent strains are not common. The long-term use of broad spectrum antibiotics is associated with some danger in that what is called "superinfection" may develop. This is due to the profound change in the bacterial flora which may develop in the nose, throat, respiratory tract, gastro-intestinal tract and urinary tract. Susceptible organisms are either diminished or greatly reduced in number. New organisms appear and there is a shift in the bacterial population. A new illness may develop due to invasion by resistant organisms, *i.e.* staphylococci, colon bacilli, *Proteus vulgaris*, *Ps. aeruginosa* or monilial organisms. Deaths have been reported due to septicæmia from these organisms and a recent report emphasized the possibility of an increase in virulence of monilial organisms during antibiotic therapy, especially in poorly nourished patients. Three deaths are reported, due to *Candida albicans* and *C. tropicalis*. Monilial abscesses in the myocardium, kidneys and lungs were the prominent post mortem features.

Hypersensitivity reactions constitute another type of hazard. Skin reactions are seen fairly frequently, especially in the case of penicillin. These are usually urticarial, but may show as morbilliform, vesicular, or bullous eruptions. Contact dermatitis may develop with penicillin and streptomycin, and is most often seen in those who are handling the drug, such as pharmacists and nurses. Ointments and oily suspensions sensitize easily. Drug fever is another sensitivity reaction which may appear about the sixth to tenth day. It is important to consider this possibility in the differential diagnosis of pyrexia of unknown origin. The temperature subsides promptly when the antibiotic is withdrawn.

Angioneurotic œdema may occur with penicillin and streptomycin and is characterized by swelling of the face, lips, tongue, and periorbital tissue and, on occasion, by difficulty in breathing. At the site of injection local œdema and inflammation are sometimes followed by necrosis. Serum sickness, as shown by fever, urticaria, eosinophilia and sometimes purpura, arthralgia, lymphadenopathy and splenomegaly may occur. It is most common with repository types of penicillin. Acute anaphylaxis is fortunately rare but may occur following a single injection in an allergic person. It may be characterized by laryngeal œdema or an acute asthmatic episode. The attack may be immediate or delayed and may be fatal if unrecognized.

Systemic disease in the form of periarteritis nodosa and disseminated lupus erythematosus has been thought in some cases to be related to long continued use in allergic persons of sulphonamides, penicillin or streptomycin. Opinion is divided in this respect.

Undesirable side reactions may occur with oral administration of antibiotic substances; thus, oral administration of penicillin may cause heartburn, nausea, vomiting and diarrhœa. However, reactions are much more common with the broad spectrum antibiotics; hence, antibiotic lozenges may cause local hypersensitivity, characterized by burning with hyperæmic patches in the pharyngeal mucosa. These substances have an inherent irritant action which is more marked with aureomycin. Thus, nausea with or without vomiting and diarrhœa may follow administration. The nauseant action may be reduced by concurrent administration of milk, food, or one of the methylcellulose products. Unfortunately, severe diarrhœa may follow in some cases. This shows as frequent liquid stools with mucus and pus. Dehydration and prostration may follow. Some diarrhœas are considered to be hypersensitivity reactions, but others are associated with the presence of coagulase positive hæmolytic strains of *Staph. aureus* in the stools in pure culture, constituting an "acute staphylococal enteritis".

Monilial infections may also occur following the use of broad spectrum antibiotics; thus, acute monilial stomatitis or pharyngitis may result. Further, pruritus due to monilial organisms may show as pruritus ani and vaginitis; thus, the casual use of broad spectrum antibiotics may give rise to several undesirable side effects.

Urinary tract complications may also follow treatment for infection in this area. The development of resistant strains with subsequent septicæmia and death has been mentioned previously. Sulphonamides may cause urinary tract complications, but new compounds are much less likely than sulphadiazine to cause crystalluria. An inadequate urinary output is the most common cause of crystalluria and hæmaturia. Caution should be used in sulphonamide administration to dehydrated patients, as massive crystallization and stone formation in the kidneys may result. Serious conditions in the form of acute glomerular lesions or tubular nephrosis

may result in renal shutdown in 10 to 14 days. Crystalluria is not present here and the anuria is probably due to hypersensitivity.

Streptomycin in the presence of renal disease, if the urine is acid, may cause albuminuria, casts, and a further decrease in renal function. In the presence of an elevated blood urea nitrogen level, the excretion of streptomycin may be retarded sufficiently to cause an unusually high blood level with an effect on the eighth nerve. These effects may arise insidiously in the use of penicillin-streptomycin combinations. Broad spectrum antibiotics in general are not harmful to the urinary tract.

With respect to the central nervous system, streptomycin has the most pronounced action, since it may cause damage to the eighth cranial nerve. Damage is proportional to the dose and duration. The auditory nerve is affected most frequently with dihydrostreptomycin, while damage to the vestibular branch of the eighth nerve occurs with streptomycin. These actions are important in the treatment of tuberculosis with streptomycin or dihydrostreptomycin.

Antibacterial agents may also affect the bone marrow, causing a depression of red and white cell elements or platelet formation. The fact that drugs have such undesirable side reactions is a calculated risk that the physician must sometimes accept. A few of the antibacterial drugs which have been reported to produce granulocytopenia are: chloramphenicol (Chloromycetin), Gantrisin, streptomycin, succinyl-sulphathiazole, sulphadiazine, sulphaguanidine, sulphamerazine, sulphanilamide and sulphathiazole.

Granulocytopenia is said to be present when the granulocyte count is in the range of 200 to 400 per c.mm. The leukocyte count is not a reliable index of a toxic effect when a drug is first being given, as agranulocytosis may develop after weeks, months, or abruptly in 12 to 24 hours.

Thrombocytopenia and hæmolytic anæmia have been produced by sulphonamide compounds. Hypoplastic or aplastic anæmia are reported to have been caused by streptomycin, sulphonamides and chloramphenicol. The possibility of toxic effects on the bone marrow due to chloramphenicol must, of necessity, cause the prescriber to hesitate in its use. The reactions reported so far have, for the most part, followed long continued use with fairly high dosage. However, symptoms may appear after a single course of medication, or there may be no apparent effect at first, toxic effects showing only on repetition of treatment. Unfortunately, many of the cases reported have terminated fatally.

In this review, an attempt has been made to stress the undesirable effects of many valuable chemotherapeutic agents. It is necessary for the prescriber to be constantly alert to the fact that all drugs have potential toxic reactions which may appear in their day-to-day usage.

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RÉSUMÉ

La thérapie aux antibiotiques est devenue compliquée par le choix des produits, la résistance des micro-organismes, le risque d'empoisonnement par le médicament (drug toxicity), et la possibilité de sensibilisation.

La pénicilline empêche les bactéries de prendre l'acide glutamique; la streptomicine dérange le métabolisme de l'acide citrique; les antibiotiques à spectre étendu empêchent la synthèse du triphosphate d'adénosine; les sulfamidés enraient les processus enzymatiques de croissance et d'emploi de substrat des bactéries.

L'effet bactéricide exige une concentration d'antibiotiques dans les tissus plusieurs fois plus élevée que pour l'effet bactériostatique.

La résistance, naturelle ou acquise, des micro-organismes est également importante, tel le staphylocoque pour la pénicilline. La résistance à la streptomicine s'acquiert rapidement (1 à 5 jours).

Le danger d'un traitement prolongé aux antibiotiques à spectre étendu réside dans l'apparition d'une nouvelle flore bactérienne résistante, et qui peut envahir l'organisme, même causer la mort. Les manifestations cutanées de la sensibilité à la pénicilline prennent habituellement la forme de l'urticaire, mais peuvent aussi causer des éruptions morbiliformes, vésiculaires, ou bulleuses.

La fièvre médicamenteuse peut apparaître du 6e au 10e jour de traitement. La pénicilline ou la streptomicine peuvent produire de l'œdème angio-neurotique. Rappelons aussi la maladie du sérum, les chocs anaphylactiques aigus, et peut-être aussi, la périartérite noueuse et le lupus érythémateux.

L'administration orale des antibiotiques à spectre étendu peut produire des nausées, des vomissements et de la diarrhée.

La suppression de la flore bactérienne habituelle permet aux champignons de causer des stomatites aigues, des pharyngites, des vaginites, et du prurit anal. Les sulfamidés ont déjà causé de la cristallurie et de l'hématurie.

Bien que les nouveaux produits soient beaucoup plus solubles que la sulfadiazine, il faut néanmoins agir avec prudence quand on les administre à des malades déshydratés.

Dans les cas où l'azote non protéinique du sang est élevée, l'excrétion de la streptomicine peut être retardée au point d'atteindre un niveau toxique pour le nerf auditif. L'action néfaste est en proportion directe de la dose employée et de la durée du traitement.

Le chloramphénicol et plusieurs sulfamidés ont déjà été impliqués dans l'étiologie de granulocytopénie.

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THE USE OF ORAL COMPOUND F (17-HYDROXYCORTICOSTERONE) IN ASTHMA*

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SINCE THE DEMONSTRATION of the beneficial effects of cortisone in bronchial asthma and other allergic conditions[1, 2] there has been a continuing interest in other substances which have the ability to suppress the disease and which might be produced with greater ease and economy. A hormone with less tendency than cortisone to produce endocrine complications, or one with equal liabilities but with a greater suppressive effect upon the manifestations of the disease would have distinct advantages in the practical management of patients. The beneficial effects of cortisone in this disease, as in most others, are usually not lasting, and maintenance of improvement is dependent upon its continuation if other forms of therapy are not used. Maintenance dosage of the hormone necessary to obtain adequate improvement varies, but as a general rule parallels the severity of symptoms. It is also true that the incidence and intensity of complicating hormonal side reactions is determined largely by the size of the maintenance dose. The chief deterrent to better results with prolonged treatment has been the development of troublesome side reactions. This limitation applies particularly to those patients with severe disease in whom maintenance requirements have been large.

It has been suggested that hydrocortisone, which differs from cortisone in only one structural detail—the presence of a hydroxy radical instead of a ketone group at the 11 carbon position of the steroid nucleus—may be the principal corticoid of this type elaborated by the adrenal gland.[3] The administration of corticotrophin (ACTH) in man has been found to be associated with the excretion of large quantities of hydrocortisone and only small amounts of cortisone.[4] It is also known that the major end-products produced by perfused normal adrenal glands are corticosterone and hydrocortisone.[5]

Laboratory studies suggest that hydrocortisone may be more physiologically active than cortisone,[6] and Thorn[7] has found that twice as much cortisone as hydrocortisone was needed to produce an equivalent eosinopenic response in a patient with Addison's disease. Hydrocortisone has been used in the treatment of other conditions with varying results. For example Boland and Headley,[8] in treating 15 patients with rheumatoid arthritis, found that free compound F was probably 50% more effective than cortisone and its tendency to produce adverse side effects was at least not greater than that of cortisone. On the other hand, patients with acquired hæmolytic anæmia showed less response to intramuscular or oral compound F acetate than to cortisone.[9]

In view of the preceding considerations, an investigation was made to determine the clinical response of patients with bronchial asthma to orally administered free hydrocortisone. Our previous experience with hydrocortisone acetate in patients with allergic disease suggested that this preparation was ineffective by mouth. The therapeutic effect of free hydrocortisone was tested in 15 cases: (1) by determining the response to an initial suppressive dose of the hormone; (2) by determining the maintenance dose of the hormone; and (3) by comparing the effects of cortisone and hydrocortisone on patients receiving both drugs.

Free compound F was administered orally to 14 patients with bronchial asthma, and one patient was switched from cortisone to free compound F (S.W., Table I). The drug was given in divided doses usually four times daily. Hydrocortisone was used in tablets of 20 mgm. while the usual cortisone tablet was a 25 mgm. one. In most of the cases in which both drugs were used, the same number of tablets was administered and this resulted in a smaller dose of hydrocortisone. The patients ranged in age from 6 to 59 years and the extent of the disease was graded from moderate to severe in type. All were treated on an ambulatory basis. Results were appraised from descriptions of improvement, from examination of the chest, and from the amount of symptomatic medication the patients required while receiving the hormone.

As a general rule the initial doses of hydrocortisone were smaller than comparable doses of cortisone, and dosage was graded according to severity of symptoms. When satisfactory clini-

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cal improvement occurred, the dosage was gradually reduced to a maintenance level.

RESULTS

The response to hydrocortisone was prompt and striking in the majority of cases (Table I). Symptoms began to subside within 24 hours in 6 patients, 36 hours in 5 patients, 48 hours in 2 patients and 72 hours in one patient. Subsequent improvement was rapid and 14 patients became reasonably free of symptoms (one in one day, 5 in 2 days, 3 in 3 days, 3 in 4 days, and one each on the fifth and sixth days). The pattern of clinical improvement was much the same with hydrocortisone as with cortisone. However, it was noticed that as rapid an onset of relief could be obtained with a smaller initial dose of hydrocortisone than of cortisone.

The lowest effective maintenance dose of hydrocortisone was determined in eight of the 15 cases of bronchial asthma. The dosage of hormone was progressively lowered until the smallest dose which would maintain the patient asthma-free had been found. As can be seen from Table I, in 7 cases the maintenance dosage varied between 20 and 40 mgm. and in one case was 80 mgm. per day. Ten of the group studied were put on maintenance doses of cortisone after a course of compound F. The duration of relief obtained following cessation of hydrocortisone therapy was observed in only five cases and found to vary rather widely. In these five patients there

TABLE I.

RESPONSE OF PATIENTS WITH ALLERGIC DISEASE TO HYDROCORTISONE ADMINISTERED ORALLY

Patient	*Age and sex*	*Diagnosis*	*Severity*	*Dosage (mgm.)*	*Days treated*	*Onset of improvement*	*Degree of improvement*	*Adverse effects*	*Lowest maintenance dosage (mgm.)*
A.A.	50 M	Asthma-intrinsic, perennial. Seasonal rhinitis	Mod. severe	120 daily for 2 days, then 60 daily	61	36 hrs.	Complete relief in 2 days	None	40
P.D.	44 M	Asthma-intrinsic, perennial	Moderate	200 daily	3	24 hrs.	Minimal symptoms within 1 day	None	*
R.D.	30 M	Asthma-extrinsic, perennial. Seasonal rhinitis.	Mod. severe	160 daily for 3 days, then progressively smaller doses	11	36 hrs.	Complete relief in 3 days	None	*
J.D.	59 M	Asthma-intrinsic, perennial	Moderate	160 daily for 2 days, then 60 daily for 4 days	6	36 hrs.	Minimal symptoms within 2 days	None	*
B.F.	6 F	Asthma-intrinsic, perennial	Mod. severe	60 daily for 2 days, then 100 daily for 4 days	6	48 hrs.	Partial relief in 2 days-complete within 4 days.	None	*
S.G.	42 F	Asthma-extrinsic-perennial	Severe	100 daily for 2 days, then progressively smaller doses	25	48 hrs.	Minimal symptoms within 3 days	Palpitations headache, rise in B.P.	40
R.K.	41 F	Asthma-intrinsic, perennial	Mod. severe	160 daily	19	72 hrs.	Complete relief in 6 days	None	*
B.K.	19 F	Asthma-intrinsic, perennial	Severe	40 daily	24	36 hrs.	Complete relief in 2 days	None	*
A.L.	29 F	Asthma-extrinsic, perennial	Mod. severe	120 daily for 2 days then progressively smaller doses	75	36 hrs.	Complete relief in 2 days	None	20
H.McK.	29 M	Asthma-mixed, perennial	Moderate	160 for 1 day then progressively smaller doses	30	24 hrs.	Complete relief in 2 days	None	40
S.S.	27 F	Asthma-mixed, perennial. Seasonal rhinitis	Mod. severe	160 daily for 2 days then progressively smaller doses	55	24 hrs.	Complete relief in 4 days	None	30
D.S.	37 F	Asthma-extrinsic, perennial. Seasonal rhinitis	Mod. severe	160 for 1 day then progressively smaller doses	60	24 hrs.	Complete relief in 4 days	Slight œdema	30
M.S.	24 F	Asthma-extrinsic	Severe	200 for 1 day then progressively smaller doses	30	24 hrs.	Complete relief in 3 days	Slight œdema	40
E.W.	41 F	Asthma-extrinsic	Mod. severe	60 daily	33	24 hrs.	Complete relief in 5 days	Slight œdema	*
S.W.	19 M	Asthma-mixed, perennial. Seasonal rhinitis	Severe	Medication changed from cortisone 100 daily to free hydrocortisone 80 daily	61		Complete relief maintained	None	80

*Not determined.
"Extrinsic" signifies non-complicated asthma due to environmental factors, usually seasonal and usually with positive skin tests.
"Intrinsic" signifies asthma, perennial in nature, usually secondary to infection and usually with negative skin tests.

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was freedom from symptoms for 7, 9, 13, 21 and 90 days respectively. Similar results were obtained with cortisone.

Total eosinophil counts were made at daily intervals. It was found that the effect of hydrocortisone upon the eosinophils was comparable to that of cortisone acetate. Depending upon the size of the initial dose, there was a drop in the eosinophil count to low levels within 48 hours in most cases. During the period that the patients were on a stable maintenance dose, it was possible to compare the effect of free hydrocortisone on the eosinophils with the effect of cortisone. Hydrocortisone was found to be more effective than cortisone acetate in the ratio of 5:4.

In two patients the urinary steroid excretion was measured* (Fig. 1). The pattern of response

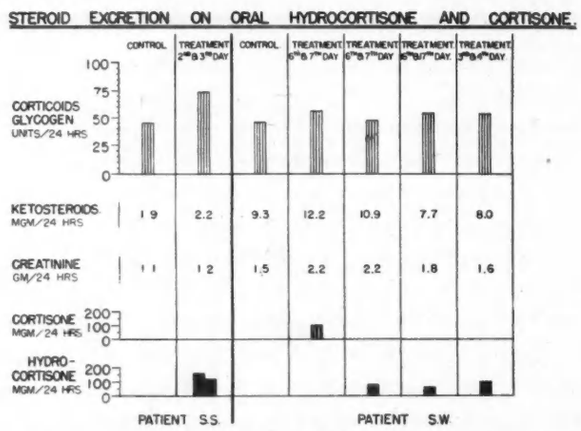

Fig. 1.—The excretion of urinary glycogenic corticoids (compound E-like) and 17-ketosteroids in two patients before and during hormone therapy.

to hydrocortisone was found to be similar to that shown by patients receiving cortisone acetate and the degree of response was roughly comparable. These results will be considered in another paper.

Despite the fact that several of the patients received hydrocortisone for as long as two to three months, few side effects were noted. Three developed slight œdema which was not troublesome, although the hormone was continued. One patient complained of headache and palpitation, associated with a transient rise in blood pressure but without œdema. Since the patients were allowed a normal diet, without the addition of salt at the table, during the period of therapy, it was felt that the incidence of side effects was low.

Several of the patients received cortisone acetate orally either just prior to or just after receiving hydrocortisone. A rough comparison was possible between the effects of these two drugs on the basis of symptoms, signs in the chest and eosinophil counts. Most of the patients noticed little difference between the two drugs and had no preference, despite the fact that the dosage of hydrocortisone was lower than that of cortisone. However, it should be noted that those receiving a smaller dose of hydrocortisone were given the same number of tablets and had no knowledge of the actual dosage difference. Therefore, as far as the patients were concerned, the treatment had not changed. Satisfactory clinical response on the part of the patient could usually be attained with a smaller daily dose of hydrocortisone than of cortisone acetate. In most cases the ratio of dosage of hydrocortisone to cortisone was 5:4 or greater (Table II).

TABLE II.

EQUIVALENT DOSAGE OF ORAL CORTISONE AND HYDROCORTISONE

Cortisone (mgm.)	*Patient*	*Hydrocortisone (mgm.)*
50	A.A.	40
150	R.D.	120
50	A.L.	20
50	H.McK.	40
50	S.S.	30
100	S.W.	80

DISCUSSION

The present study indicates that, when administered orally to patients with bronchial asthma, hydrocortisone is highly effective in suppressing the disease and maintaining control of it. The pattern of improvement with initial suppressive doses was, in general, similar to that observed with oral cortisone. The response to hydrocortisone was found to be just as rapid, and even though smaller doses were used clinical improvement was as great as with cortisone. These observations suggest that hydrocortisone may be more effective, milligram for milligram, in suppressing the manifestations of bronchial asthma and that smaller amounts of the hormone may be required to control the disease. Rapid relief of asthma has been achieved with much higher doses of cortisone of the order of 200 to 300 mgm. as an initial dose, followed by 50 mgm. every four hours until the symptoms subside. This regime usually brings relief within 4 to 8 hours. Although this type of schedule was not tried with hydrocortisone, there is no reason

*We wish to thank Dr. E. H. Venning for these determinations.

to suspect that an initial dose of 160 to 240 mgm. followed by 40 mgm. every four hours would not produce the same result. Despite the greater potency of hydrocortisone it is not accompanied by a correspondingly greater tendency to produce complicating side reactions, and the tendency may even be less. These observations suggest that hydrocortisone may prove to be a better therapeutic agent for bronchial asthma than cortisone acetate. However, in comparison with cortisone, hydrocortisone offers few clinical advantages as determined by these and other studies. It could be used in preference to cortisone only if the cost of the drug were substantially lowered.

Although the primary purpose of this paper is to compare hydrocortisone with cortisone, it must be emphasized that the clinical use of either compound should be reserved for those cases which do not respond to the older methods of treatment. Similarly the contraindications and precautionary measures apply just as much to the use of hydrocortisone as to cortisone. These have been emphasized in other publications and will not be dealt with here.

SUMMARY

Fifteen cases of asthma were treated with oral hydrocortisone. The response to therapy was found to be similar to that observed with cortisone, although smaller doses of hydrocortisone were usually required. Side effects were no greater than with cortisone and the duration of relief following cessation of therapy was similar. Hydrocortisone could be used in preference to cortisone only if the cost of the drug were substantially lowered.

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LONG-TERM CORTISONE THERAPY IN RHEUMATOID ARTHRITIS

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THE DEMONSTRATION by Hench *et al.*[1] that cortisone exhibits anti-rheumatic properties stimulated this investigation of the usefulness of the agent in long-term treatment of rheumatoid arthritis. Since the initial announcement in 1949, many reports have been made confirming the anti-rheumatic effects of cortisone but only a few authors have reported on its long-term use in rheumatoid arthritis.

Boland[2] reported in 1951 on a group of 76 patients started on cortisone between January 1, 1950, and August 31, 1950. In this group there were 31 males and 45 females, ranging from 19 to 80 years of age. The majority (56) had peripheral rheumatoid arthritis; 20 had rheumatoid spondylitis, three without and 17 with peripheral joint involvement. Out of this group of 76, cortisone therapy was discontinued in 16 patients after less than six months, chiefly because of an initial poor response or because of side effects. The remaining 60 patients received cortisone for six to 15 months. Their improvement was graded as "very marked" in 18 patients; "marked" in 30 patients; "moderate" in 11 patients; and "slight" in one patient. Therefore, 48 patients out of 76—or just less than two-thirds—received marked or very marked benefit from cortisone administration. The author states that the results were poorer in severe cases because of the large dose needed for control of their disease.

Also in 1951, a report was published by Ward *et al.*[3] on their first 100 cases of rheumatoid arthritis in which oral cortisone was administered. Twenty-seven of these patients received cortisone intramuscularly "for a variable period" and then changed to oral cortisone; 72 patients received oral cortisone throughout for periods of one to 12 months; one patient was first given oral cortisone and later changed to the intramuscular form when he failed to respond. Of the 73 patients to whom cortisone was administered orally, the "relief of symptoms" was graded as follows: "very marked" in 19; "marked" in 28; "moderate" in 25; and "none" in one patient. The authors did not report whether or not cortisone had to be stopped because of side effects but in 11 cases it was discontinued to see how much improvement would be maintained. Relapses soon occurred in nine of these 11 cases on withdrawal of cortisone.

In 1952, Copeman and co-workers[4] reported on the use of cortisone in a group of 20 rheumatoid arthritics under observation from three to ten months. They were originally "concerned in devising a suitable method of administration which will suppress the disease indefinitely and enable the patients to resume useful and independent lives, free from unpleasant side effects." Their group of patients had had active rheumatoid arthritis for at least six months and usually longer. The results of treatment were listed as follows: "good" in twelve; "fair" in five; and "definite but poor" in three

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patients. Only one case had side effects necessitating cessation of cortisone therapy. They stated that their results could probably have been further improved—on a lower dosage and, therefore, with fewer side effects—if earlier cases without joint damage had been selected.

At the American Rheumatism Association meeting in 1952, Bauer[5] commented on the results of cortisone and ACTH treatment in 48 cases of rheumatoid arthritis. These patients were treated for from eight to 680 days. He concluded that there was "usually striking subjective improvement with less striking objective improvement". There were no lasting remissions; in fact, in some instances progression occurred. The beneficial effect of cortisone and ACTH was attributed to the controlling of stiffness, aching and pain, thereby permitting functional improvement. Bauer stated that these hormones should never be solely relied upon in the management of the disease.

The project reported here was started in February, 1951, when the supply of cortisone warranted more extensive clinical evaluation. We were particularly interested in assessing its value as an aid to rehabilitation when used in conjunction with the standard basic program of rest and remedial physiotherapy.

It was decided to study a specially selected small group of patients over a prolonged period of time. This study was carried out in two separate arthritis clinics, one of which initially undertook to treat patients with intermittently administered cortisone, while the other was to use continuous therapy. Thirty-nine patients were treated, of whom 27 were started on the intermittent regimen and the remaining 12 were given cortisone continuously. Of the 27 started on intermittent therapy, six were changed to continuous maintenance dosage, usually after a minimum period of 8 to 12 months of intermittent administration of the hormone, and are included in both groups. It is probably worthy of mention that all patients included in this project were attending a general hospital outpatient department and thus are in a different socio-economic group from the general rheumatoid arthritic population.

Selection of patients.—The main criterion in the selection of patients was potential reversibility of the disease and hence capacity for rehabilitation to gainful occupations. Thus, no patients with crippling deformities or advanced multiple joint destruction were included. All patients had had rheumatoid disease for at least six months and the shortest time any had been in an active phase of their disease was four months. Cases of both rheumatoid arthritis and rheumatoid spondylitis were included. All patients in the group were otherwise in essentially normal health except for one who had minimal bronchiectasis and another who has mild bronchial asthma. Chest radiographs and electrocardiograms were taken prior to treatment and these were normal in all cases.

Age and sex.—The youngest patient was 20 and the oldest 60 years of age. In the intermittently treated series, the average age for males was 46 and for females, 40 years of age. In the continuously treated group, the average for males was 45 and for females, 39 years. The overall average was 42 years of age.

In the combined group there were 23 males and 22 females. Of this total, two males and four females were transferred from the intermittent to the continuous series. The unusually high proportion of males is partially explained by the fact that when the male breadwinner becomes unable to work he quickly becomes eligible for outpatient department attendance.

Type of disease and duration of activity.—Out of the 39 patients treated, 30 had rheumatoid arthritis and nine had rheumatoid spondylitis. Seven of the spondylitics had peripheral joint involvement. Duration of rheumatoid disease varied from five to eight years with an average of six years in the group treated continuously. In this group, the duration of the present attack varied between two and three and one-half years with an average of three years.

Duration of rheumatoid disease varied from one-half to 16 years with an average of eight years in the intermittently treated series. In this series, the present attack was of one-half to 16 years' duration, with an average of six years.

TREATMENT

Most patients were seen at least every two weeks, at which time they were briefly checked in regard to the status of their disease and possible side effects. Hæmoglobin value, sedimentation rate, and white cell counts were determined and urine was examined frequently. Prior to therapy and every three months while on therapy, a complete physical examination was carried out and the status of the disease was assessed in detail. Biochemical studies were not made except when clinically indicated, and were rarely necessary. Glucose tolerance tests were done on six patients after prolonged treatment and the results in all were within normal limits.

Prior to initiation of therapy, all patients had been on a basic treatment program consisting of increased rest, supervised exercise therapy and

supportive measures and these were carried on throughout the project. Social casework studies were done on most patients at some time during their treatment. Several patients were admitted to a rehabilitation centre for an average period of one to three months, where a closely supervised basic program of treatment could be carried out.

TABLE I.

AGE, SEX AND DURATION OF DISEASE

	Total*	Age (years)	Duration of disease (years)	Duration of present attack (years)
A. Intermittent therapy:				
Male	12	46	6½	5
Female	15	40	9	6
B. Continuous therapy:				
Male	11	45	5	4
Female	7	39	8	2

*A total of 39 patients are included in this review, six of whom are included in both the intermittent and continuous series.

In this study, oral cortisone (Merck & Company) was used almost exclusively. In the early stages of the continuously treated series, cortisone was given in initial doses of 100 to 150 mgm. per day and then gradually tapered down to maintenance doses. As more experience was gained, patients were started on lower doses, usually between 75 and 100 mgm. daily. It was soon found that it was impractical to attempt to suppress symptoms completely and a maintenance dose was adopted which would reasonably suppress the subjective manifestations of the disease and allow adequate physiotherapy without serious signs of overdosage. It was found that doses from 50 to 75 mgm. daily were usually adequate although occasionally higher doses were given for short periods of time in an effort to suppress exacerbations of the disease. Thus, in this series, the average dose of cortisone given per month varied from a maximum of 2.38 gm. to 1.33 gm.

Of the 18 patients treated continuously, two received cortisone for three and five months respectively; seven for six to 12 months; five for 12 to 24 months; and four for 24 to 28 months.

In the intermittently treated series an initial course was given in a sufficient daily dosage and over a sufficient period of time to achieve a maximal suppression of the disease process. Usually this required three to four gm. of cortisone at a daily dose of 75 to 100 mgm. After the initial course had stopped, the patients were observed at frequent intervals and booster courses were instituted whenever a recurrence of activity of the disease indicated. These courses usually consisted of one-half to two gm. at 75 to 100 mgm. per day. Eventually it was learned that gradual tapering off of cortisone was usually preferable to the sudden withdrawal of the drug practised in the beginning.

The amount of cortisone used per month varied from 0.34 to 1.56 gm., except for one patient who required 2.93 gm. per month. Eighteen patients received cortisone intermittently for periods ranging from 13 to 25 months. The remaining nine were on treatment for four to eleven months. Six of the total were changed to continuous therapy after the intermittent regimen had been tried and found unsuccessful, usually after eight to 12 months.

Intra-articular hydrocortisone was used in 14 of these patients, usually when one or a few joints appeared resistant to the oral dose of cortisone being given. It is felt that this treatment did not materially alter the eventual results. Four cases had received some benefit from gold therapy prior to starting cortisone and it was continued in maintenance dosage. An additional five were started on gold injections later on during the experiment; in only one case could any definite beneficial effects be ascribed to this and there was never any evidence of ill effect due to addition of gold therapy.

RESULTS

The criteria* of the American Rheumatism Association were used in assessing the activity, the stage of the disease and the response to therapy. According to this classification the results were disappointing. It is pointed out, however, that these patients were selected from an out-patient department clinic and this may have had some influence on the results. Further, this classification, being purely objective, places emphasis on joint changes and not on the response of the patient as a whole.

In the continuously treated series only one person (5%) achieved a Grade I response, this being a male with low-grade rheumatoid

*The American Rheumatism Association "Therapeutic Criteria for Response of Rheumatoid Activity" are based entirely on objective evidence. Briefly, Grade I response indicates complete remission; Grades II and III response indicate major and minor improvement respectively; Grade IV response indicates no improvement or progression of the disease. Further details regarding this classification are available elsewhere.

spondylitis who went into a complete remission after three months' therapy. Three patients (17%) gave a Grade II response; twelve (67%), a Grade III response; and two (11%), a Grade IV response. Sex did perhaps play a significant part in these results in that four who gave a Grade II or better response were all males.

Of the 27 patients in the intermittently treated series, none had a Grade I response to treatment, or complete remission. Grade II response to treatment, or major improvement, occurred in nine or 33% of the cases: six of these were males out of a total of 12 (50%) and three were females out of a total of 15 (20%). Grade III response, or minor improvement, occurred in seven or 26% of the total cases: three of these were males (25%) and four were females (27%). Grade IV response —*i.e.*, no improvement or worsening of the disease—occurred in 11 or 41% of the total cases: three of these were males (25%) and eight were females (53%).

TABLE II.

RESPONSE TO TREATMENT

	A. Intermittent						*B. Continuous*					
	Males	*% of males*	*Females*	*% of females*	*Total*	*% of total*	*Males*	*% of males*	*Females*	*% of females*	*Total*	*% of total*
Grade I	0	0	0	0	0	0	1	9%	0	0	1	5%
Grade II	6	50%	3	20%	9	33%	2	18%	1	14%	3	17%
Grade III	3	25%	4	27%	7	26%	7	64%	5	72%	12	67%
Grade IV	3	25%	8	53%	11	41%	1	9%	1	14%	2	11%

DISCUSSION

In analysing the results, the following factors are considered: age, sex, duration of rheumatoid disease and present attack, activity of the disease at the beginning of treatment, complications and reasons for discontinuing cortisone.

Age.—When the average for the whole group is considered, there does not seem to be any relationship between age and response to treatment.

Sex.—A higher proportion of the male group responded well, in that 43% of males in the whole series achieved a Grade II or better response, whereas only 17% of females did likewise. Conversely, 44% of females gave a Grade IV response whereas only 20% of males fell in the same category. It is possible that this apparent sex variation is of no significance in such a small group.

Duration of activity prior to therapy.—There seems to be a definite correlation between the duration of activity prior to treatment and the response to therapy. Six out of nine patients (66%) whose disease had been active for less than two years prior to treatment gave a Grade II or better response, whereas only five out of 30 patients (17%) with activity for over two years gave a similar response.

Type of disease.—Nine patients with rheumatoid spondylitis were treated and the overall response to both forms of therapy was not significantly different when compared with the series as a whole. It was, however, the impression of the authors that the subjective response was greater than in those with rheumatoid arthritis.

Complications.—Fluid retention was the only major sign of overdosage of note. This was encountered in 33% of the entire series: 50% of the continuously treated group and 25% of the intermittently treated group, but in none was it severe enough to warrant discontinuing cortisone and was usually controlled by lowering the dose and restricting salt. This difference in incidence is directly related to the average monthly consumption of cortisone. Three patients had psychotic episodes while under observation. One was transient and therapy was later re-instituted. Of the other two, cortisone had been discontinued in one at her own request a year previously and the second had only two one-gram booster courses in the year preceding a definite psychiatric diagnosis.

Varying degrees of moon-face, acne, hirsutism and menstrual irregularities were encountered from time to time during the project but were never a major problem and did not interfere with therapy. Two cases of phlebothrombosis of deep calf veins occurred in the intermittently treated series, necessitating temporary discontinuance of

therapy. Both of these patients were ambulatory and doing remedial exercises at the time.

Reasons for discontinuing cortisone.—Cortisone was discontinued in 13 cases. One of these was for a minor psychotic episode and it was restarted without recurrence of the mental upset. Another was for a major psychotic manifestation and cortisone was not restarted. In one case cortisone was discontinued one month before lobectomy for bronchiectasis as it was felt that it had not significantly affected the course of the patient's rheumatoid disease. One month postoperatively it was restarted because of an exacerbation. Two months subsequently he developed fever, hypotension and rales in his right lower chest and died within twelve hours. The cause of death was not ascertained because it occurred in a rural hospital, but probably adrenal suppression played a major part in the hypotension and fatal outcome. In one case cortisone was stopped because of persistent albuminuria, the cause of which has not yet been determined.

In three cases treatment was discontinued at the patient's request; all of these patients were females with unstable personalities and were, in retrospect, unsuitable candidates for the project. In two cases it was discontinued because of poor response. One of these patients had sclerodactylia and rheumatoid arthritis. The other had rheumatoid spondylitis together with involvement of both knees. It is interesting to note that the condition also proved refractory to large intra-articular doses of Compound F. In only four cases was cortisone discontinued because of partial or complete remission of the disease.

CONCLUSIONS

It is feasible to give patients with rheumatoid arthritis long-term cortisone treatment without undue incidence of serious toxic effects, provided adequate clinical supervision is maintained. It appears that such therapy is more beneficial in patients who have had their disease for a relatively short period of time. Those with severe rheumatoid activity require too large doses of cortisone to warrant its being given continuously, because of the risk of serious complications. On the other hand, there seems to be a group of patients with low-grade activity who do well with continuous low-dosage therapy. It is, however, neither practical nor safe to use doses large enough to suppress symptoms completely. There is no doubt that, in the majority of patients, it produces symptomatic improvement but does not seem to influence the underlying pathological physiology. It is a useful adjunct to a standard basic program of increased rest and physiotherapy and allows earlier rehabilitation. It is concluded that treatment has to be individualized both as to dosage and as to schedule of administration. There seems to be merit in either continuous or intermittent therapy in different individuals.

Although results, as judged by the American Rheumatism Association classification, have been disappointing, this does not reflect the overall symptomatic response, and partial or complete rehabilitation has been achieved in a significant number of patients. Table III shows the employability statistics before and after therapy. It will be noted that the number of unemployable persons was reduced from 24 to six. The number of employed persons increased from three full-time and twelve part-time before therapy to 15 full-time and six part-time after therapy. It is not our wish to infer that these results are entirely due to cortisone therapy. A large measure of success in rehabilitation of arthritics is due to the assistance of medical social caseworkers, rehabilitation counsellors and employment agencies.

TABLE III.

EMPLOYABILITY OF 39 PATIENTS BEFORE AND AFTER THERAPY

	Unemployed				*Employed*	
	Unemployable	*Employable*	*Under Treatment*	*No Record*	*Full-time*	*Part-time*
Before	24	–	–	–	3	12
After	6 (inc. 1 dead)	8	2	2	15	6

With proper selection of cases and adequate supervision, the incidence of major complications is not sufficient to render prolonged cortisone therapy dangerous. In this age group, apart from varying degrees of fluid retention, psychological abnormalities were the most significant complication and these usually can be avoided by proper selection of patients.

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RÉSUMÉ

A la suite des travaux de Boland, Ward, Copeman et Bauer, les auteurs entreprirent, en février 1951, le traitement de l'arthrite rhumatoïde au moyen de préparations de cortisone à action prolongée.

Vingt-sept malades reçurent un traitement intermittent, et douze un traitement continu. Le choix des sujets fut basé sur leur potentiel d'amélioration. Certains cas de spondylite furent inclus. On choisit vingt-trois hommes et vingt-deux femmes, malades dont les âges s'échelonnaient de 20 à 60 ans.

Une évaluation méthodique des malades fut faite avant et pendant le traitement. La cortisone sous forme de comprimés fut employée presque exclusivement, en doses de 100 à 150 mgm. par jour au début, réduite ensuite à 50 à 75 mgm. Chez les malades traités d'une manière intermittente, on observa que la diminution graduelle des doses était préférable à l'arrêt brusque du médicament.

Quatorze malades reçurent des injections intra-articulaires d'hydrocortisone, lorsqu'il fut constaté qu'une ou plusieurs articulations ne semblaient pas réagir au traitement oral.

Si l'on évalue les résultats d'après les barèmes de l'Association américaine du rhumatisme, ceux-çi ne sont pas encourageants. Les hommes accusèrent une amélioration plus fréquemment que les femmes. Il semble y avoir corrélation entre l'activité de la maladie avant le traitement et le résultat du traitement. A une phase ou à une autre du traitement, un tiers des malades firent de la rétention hydrique. Trois malades donnèrent des manifestations de psychose. La cortisone ne fut arrêtée pour cause de rémission complète ou partielle que dans 4 cas seulement. Les doses nécessaires pour effectuer la suppression complète des symptômes ne sont ni pratiques ni sans danger.

METASTASIZING BRONCHIAL ADENOMAS*

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THE CLINICAL PATHOLOGICAL entity currently styled "bronchial adenoma" was first described by Laennec[20] in 1831. This author's discovery was confirmed and enlarged upon by Mueller[32] in 1882. After this initial work, little was contributed on the subject until the early 1930's when Geipel[13] was able to review only six reported cases. In the following two decades, interest in this tumour and its associated symptomatology increased markedly, particularly since advances in thoracic surgery offered a potential cure.

In 1941, Foster-Carter,[11] published a very thorough review of the literature including the pertinent clinical and pathological findings in 70 cases. The consensus at that time was that the tumour was benign although some histological features of malignancy were conceded. The presence of atypical mitoses, cell hyperchromatism, local infiltration of bronchial wall and lymphatic permeation were considered evidence of local malignancy. Some authors believed that adenomata occasionally underwent malignant change, giving rise to typical bronchogenic carcinoma.[7, 34] Foster-Carter,[11] Kramer,[19] Clerf,[6, 7, 8] and Jackson[18] all felt that, although occasionally locally malignant, bronchial adenoma never gave rise to "distant metastases". This belief dies hard and as recently as 1949, it was stated[27] that distant metastases had never occurred.

A case is reported below which fulfils the histological criteria of bronchial adenoma, together with an unusual and obviously hæmatogenous metastasis.

CASE REPORT

Mrs. A.H., 67, was admitted to hospital for investigation of bouts of acute epigastric and right upper quadrant pain. An exacerbation of her condition three days before admission gave rise to excruciating pain, and in view of her associated intolerance to fatty foods a provisional diagnosis of biliary colic was made.

The past history was of considerable interest in view of the subsequent findings. Approximately 25 years before the patient's terminal illness, she was in hospital for 16 weeks because of a right-sided pleurisy with effusion which was apparently never proven specific.

On examination, the abdomen was markedly tender, with guarding in the right upper quadrant. No rebound tenderness was elicited and no abnormal masses or visceromegaly was discovered. Accordingly, the gall-bladder was examined roentgenologically and found to be only partially functional with numerous small cholecliths present. The right chest showed minimal reduction in movement, with diminished breath sounds and impaired vocal fremitus and resonance. A chest radiograph revealed notable cardiac enlargement with a minimal increase in markings in the left lung field and a completely opaque right lung field to the level of the 4th rib anteriorly. The radiologist reported marked cardiac enlargement and also evidence of infiltration within the right lobe. The possibility of fluid in the right pleural cavity could not be excluded.

The blood pressure was 175/130 with a pulse regular in rate and rhythm at 90. An electrocardiogram showed evidence of an enlarged left ventricle and auriculo-

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ventricular block. The hæmogram, prothrombin time, serum bilirubin and urine were within normal limits on admission.

Cholecystectomy was carried out without undue difficulty eight days after admission. The finding of small pigment choleliths and a thickened gall-bladder prompted exploration of the common duct, but it contained no stones and Archibald dilators were passed with ease into the duodenum. The pathological report confirmed the presence of chronic cholecystitis with cholelithiasis.

The immediate postoperative course was uneventful. Approximately 12 hours after operation, it was noted that the patient had developed a tachycardia and an irregularity in pulse rhythm. The blood pressure rose precipitously to 245/130. During the following three days, the patient developed oliguria which progressed to absolute anuria with ensuing azotæmia. Her condition rapidly deteriorated and after a short period of semi-coma with Cheyne-Stokes respiration, she died.

Fig. 1

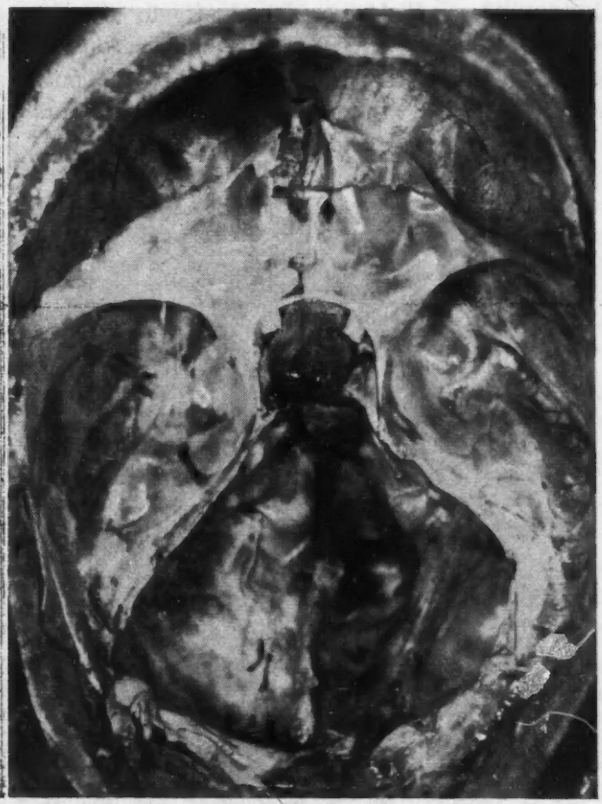

Fig. 2

Fig. 1.—Bronchial adenoma of right lung. Nubbin of smooth tissue projecting into main bronchus with large "ice-berg" tumour involving most of the lobe. **Fig. 2.**—Secondary bronchial adenoma—pituitary fossa.

AUTOPSY FINDINGS

The pertinent findings were as follows:

The right pleural space was completely obliterated by dense fibrous adhesions. The right lung weighed 380 gm., and the bronchial tree revealed a mass of firm pale yellow tissue completely blocking the right lower lobe bronchus at its origin. On section of the lung, a large pink mass 10 cm. in length by 4 cm. in diameter was seen to make up most of the tissue in the atelectatic right lower lobe (Fig. 1). The tumour was well circumscribed and extended downward like an iceberg from the tissue occluding the right lower lobe bronchus. The tissue in the tumour was for the most part extremely friable and in areas gelatinous. Throughout its substance, however, fine spicules of bone gave the impression of "egg-shell" crackling. The remaining portions of both lungs were extremely wet, and fluid exuded from the cut surface.

The heart showed left ventricular hypertrophy and some patchy interstitial fibrosis but was not otherwise remarkable. Section of the left adrenal showed that it contained a yellow cortical adenoma 1 cm. in diameter.

The brain weighed 1,240 gm. and on serial section appeared normal. The sella turcica was tremendously enlarged, with a bulging mass beneath the diaphragma sellæ (Fig. 2). From the sella, a large mass of soft purple gelatinous tumour tissue was evacuated, leaving a space two cm. in depth. The tumour tissue was remarkably similar to the gelatinous tissue found in the previously described bronchial tumour.

The gross diagnosis of cardiac hypertrophy with interstitial fibrosis, pulmonary œdema, passive congestion of the liver and a marked degree of nephrosis were confirmed histologically.

Many sections from the bronchial tumour were examined and a somewhat variable picture was encountered in its different parts. For the most part, the tissue was made up of very uniform small hyperchromatic cells with circular nuclei and scant eosinophilic cytoplasm. These cells were widely separated, with only an occasional delicate strand of reticular support (Fig. 3). Other areas contained many spicules of bone and frequent capillaries in a denser fibrous connective tissue stroma (Fig. 4). In other areas, rosettes of cells forming poorly defined pseudoacini were seen. The remaining areas were typical of the so-called cylindromatous type of bronchial adenoma with a solid trabecular structure. There was no pleomorphism, and mitotic figures were conspicuous by their absence.

Sections from the tumour occupying the sella turcica were histologically similar to the majority of areas in the bronchial adenoma although no cylindromatous type of formation or osseous metaplasia was encountered.

The adrenal tissue showed a moderate degree of hyperplasia with the typical histology of a cortical adenoma.

DISCUSSION

Since bronchial adenomas account for between 6 and 10% of primary neoplasms of the lung,[21, 27] pathologists in hospitals with an active thoracic unit will be called upon frequently to give an opinion on this tumour. It seems reasonable therefore to attempt a comparison of the now well authenticated adenoma with those tumours known to be associated with metastases.

The ultimate symptoms are those of absolute obstruction and concomitant atelectasis and infection. Adenomas however, have a notoriously long history.[4] Cough, hæmoptysis and chest pain usually precede the atelectasis by at least 2½ years. Many of the patients give a long history of repeated bouts of pneumonia, and indeed Anderson[2] states that any tumour 5 cm. or over has been present at least 8 years.[35] The majority of tumours because of their position close to the origin of major bronchi are readily accessible to bronchoscopic examination. The tumour covered by intact mucosa, usually projects as a thumb-like process into the lumen. Only a few are confined to the lumen and the immediate

Fig. 3

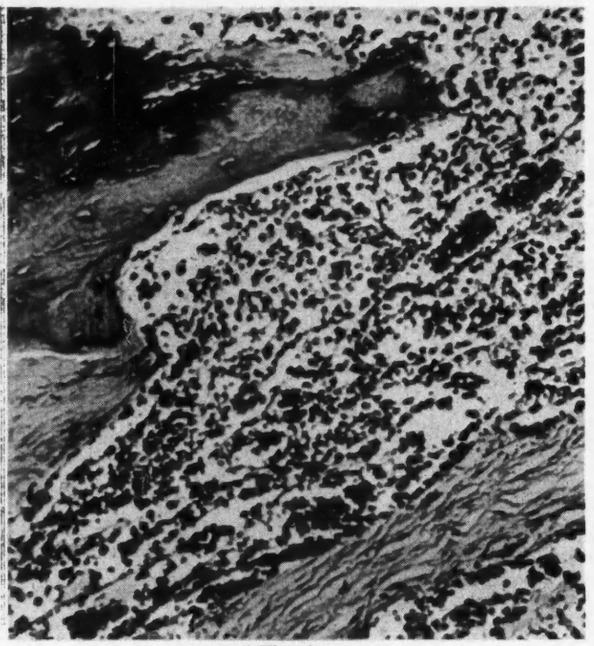

Fig. 4

Fig. 3.—Bronchial adenoma. x400. Fig. 4.—Metaplastic bone—bronchial adenoma. x200.

Bronchial adenomas are seen chiefly in the 3rd and 4th decades, although in Rabin's series[28] of 64 cases, the average age was only 28. The sex incidence is an important diagnostic feature, since women are equally susceptible to the development of adenoma, while only 10 to 20% of cases of bronchogenic carcinoma develop in the female. The adenoma nearly always develops in the main stem bronchi close to their origin and particularly the right lower lobe bronchus. A few reported cases of peripheral development of bronchial adenoma associated with bronchial adenomatosis are the exception to this general rule.[10]

peribronchial connective tissues. This connective tissue forms a capsule contiguous with the tumours, no matter what their size. In many cases, although the endobronchial mass of tissue is small and even pedunculated, the greater part of the growth pushes deeply into the respiratory parenchyma in the fashion of an iceberg.

Several classifications and many names have been proposed because of the histological variations in bronchial adenoma. The confusion has been such that Liebow was able to advance 27 given synonyms and related terms.[28] There appears to be increasing agreement that only two major histological patterns exist, namely the cylindromatous and carcinoid variants.[17, 28, 31]

The use of the term "mixed tumour"[7, 15] for bronchial adenoma has no more histological validity than when this misnomer is applied to the pleomorphic salivary gland adenoma, and in the lung should be further condemned since it does not enjoy the long usage of the term denoting the adenoma of the salivary gland. Bone, often seen in these tumours, has been construed to represent an integral part of the neoplasm but it is now thought to represent stroma metaplasia and not to be a true part of the neoplasm.[3, 21, 30] Even the superficial resemblance to salivary gland adenoma is open to question since myoepithelial nests, pseudochondromatous change, and myxomatous degeneration have not been described in the stroma of the bronchial tumours.

In the carcinoid variant, the cell pattern is one of solid epithelial masses, composed of polyhedral cells with small, relatively hyperchromatic, circular nuclei and clear slightly granular cytoplasm. Areas of the tumour may be histologically indistinguishable from the primary carcinoid tumours of the ileum and appendix. It is however rare to demonstrate the presence of argentophilic granules in the cytoplasm. Hamperl[17] in 1937, reported what he believed to be the only case showing affinity to silver stains. More recently, Holly, in a series of 34 carcinoid type of bronchial adenomas, found argentophil granules in only one instance. The solid columns and masses of the carcinoid tumour occasionally give way to poorly differentiated acini or form a trabecular pattern with pseudo-acini.

Recently, the oncocytoid variant has been described by Hamperl[16] and by Stout.[30] This particular tumour consists of sheaths of extremely large cells with abundant, slightly granular, striated cytoplasm and small, centrally placed, hyperchromatic nuclei. On occasion, a trabecular arrangement with a double layer of these so-called oncocytes is seen.

The second major histological pattern, the cylindromatous form of bronchial adenoma, presents a strikingly different histological appearance; in contrast to the marked regularity of the carcinoid form, it is slightly more pleomorphic with some nuclear variation as regards both size and staining qualities. The cell arrangement is on occasion strikingly like that of epithelioma adenoides cysticum[12] with a plexiform mass of basal-like cells, occasionally showing keratinization. It is generally agreed that this type of tumour is more locally malignant than the carcinoid variant and it has been likened to the cylindromatous tumours of the submaxillary gland which infiltrate nerve sheaths and lymphatics with fairly constant spread to regional nodes.[9] A rare variant of the cylindroid form is the muco-epidermoid bronchial adenoma in which sheaths of epithelial tissue are intermingled with well differentiated mucous glands.

The question of malignancy with metastases is one of relatively recent interest, stimulated first by Adams[1] in 1942, when in describing five cases of bronchial adenoma he reported one with involvement microscopically of liver and vertebræ. In the same year, Anderson[2] reported a case of bronchial adenoma with a nodule 2 cm. in diameter in the liver which was histologically identical with that seen in the right main bronchus. Since that time, many authors have reported small series and individual cases of bronchial adenoma with metastases, and a review of some 25 of these cases appears in Table I.

From the review of these cases, it is apparent that the age incidence of the metastasizing tumours is approximately 10 years older than for those not exhibiting this phenomenon, although Rabin[28] in a small series felt that those tumours which metastasized were in an even younger group. The average age in this series is 45 years. There is absolutely no sex variation; 12 of the tumours were in males and 13 in females. As in the benign form, the lesion tends to develop a few years earlier in females.

The sites of predilection for metastatic spread appear to be the regional lymph nodes, bone marrow, the same or the opposite lung, and the liver. This finding is identical with that for site incidence of metastases from bronchogenic carcinoma.[21] Many authors have made much of the fact that most cases show only hilar lymph node involvement. It would seem that this distinction is rather artificial, since node involvement in any malignant growth is a precursor to blood stream invasion. The liver appears to be the most commonly involved parenchymal organ. This is not too surprising when it is remembered that the liver is a favourite site for secondary systemic metastases despite its relatively poor arterial blood supply.[33] Systemic metastases are more commonly located in the liver than in the lung.

Although the majority of reports are clinical descriptions of the lesion with only the bare pathological findings, it would seem that most of

TABLE I.

Author	*Age*	*Sex*	*Site*	*Metastases*
Goldman[14]	58	M.	Trachea	Pericardium, pleura, lungs, lymph nodes
"	30	F.	R.M.B.	Hilar nodes
"	60	M.	R.M.B.	Hilar nodes
Sano[29]	57	M.	R.U.L.B.	Lung
Anderson[2]	40	F.	R.M.B.	Liver
Moersch[25]	15	M.	R.U.L.B.	Hilar nodes
Moersch[26]	49	M.	R.M.B.	Liver and hilar nodes
"	67	M.		Liver
"	34	F.		Lung
Laff[22]	40	F.	R.M.B.	Hilar nodes and lung
"	45	F.	L.M.B.	Lung
Chamberlain[24]	47	M.	R.L.L.B.	Hilar nodes
"	32	F.	R.L.L.B.	Hilar nodes
"	23	F.	R.L.L.B.	Lung
"	43	F.	L.M.B.	Lung
Adams[1]	62	F.	R.L.L.B.	Bone marrow
"	47	M.	R.U.L.B.	Hilar nodes
"	36	F.	Trachea	Mediastinal nodes and liver
Womach[34]	43	F.	R.M.B.	Mediastinum
"	53	M.	L.M.B.	Hilar nodes and lungs
Van Hazel[31]	53	F.	R.M.B.	Kidney, lungs and hilar nodes
Mallory[23]				Hilar nodes
Cheek[5]	44	F.		Pericardium, pleura, lungs, adrenals and lymph nodes
Stowell[15]				Hilar node
Graham[15]		M.	R.L.L.B.	Liver and lung
"	42	M.	L.L.L.B.	Liver and hilar nodes
Geever[12]	74	M.		Liver and hilar nodes

these tumours histologically fall into the cylindromatous group. Even when the histological description might lead to the belief that the tumour is of the carcinoid type, there is usually more pleomorphism in some areas of the tumour than is generally seen in the gastro-intestinal counterpart. In Cheek's[5] case, the centre portion of the tumour was carcinoid-like while the periphery produced a pattern approaching that of alveolar cell carcinoma.

One of Goldman's[14] cases was remarkable for the coincidental presence of pituitary and adrenal adenomas, suggesting a widespread tendency towards neoplasia. The presence of a large adrenal adenoma in the case presented here would lead to a similar assumption.

From this review we may conclude that metastasizing bronchial adenoma has a natural history as regards time, sex and histological pattern identical with those tumours which have not metastasized. It would appear that there is no way in which clinical or histological study can show the degree of malignancy. On this basis alone, I would feel that there is no place for endoscopic resection, except for biopsy. Indeed, except in patients markedly debilitated by associated obstruction and infection a radical operation would seem to be the procedure of choice.

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THE FATE OF THE LIVER IN CHRONIC ALCOHOLICS*

PART I.—BROMSULPHALEIN TEST AS AN INDEX OF HEPATIC DYSFUNCTION IN ALCOHOLICS

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THE PROGRESSIVE DETERIORATION of the liver in chronic alcoholics is hardly disputable. To add that it is the most frequent and most consequential of physical complications following alcohol overindulgence would be a clinical truism. About one and a half years ago, in a preliminary work,[1] we attempted a screening of this abnormality in our patients by means of liver function tests, and we found that it may occur in the very first years of alcoholism. Other authors have used various laboratory tests for the same purpose.[2, 3, 4]

Of the numerous liver function tests available to the clinician, only the bromsulphalein (BSP) one was retained in our study. It has proved to be the most reliable index in the screening of the slightest dysfunction (usually unnoticed upon clinical examination) and in the objective appraisal of treatment. It is noteworthy that, in the great majority of our cases, such dysfunction would have escaped clinical investigation, had there not been a clue in the progressive decreased intolerance to alcohol in most patients. The subjects themselves state that they "can't take it" as before and, with amazing if not scientific accuracy, put the blame for it on their liver.

In the group of 45 patients in our preliminary paper,[1] 23 (51%) had a BSP retention greater than 5% after 30 minutes, value which is considered as the upper limit of normal by most investigators (with the 5 mgm. dose per kg.). These data were confirmed later on by McBroom and Smith[5] who found out that approximately half of their 40 patients had abnormal BSP retention.

EXPERIMENTAL

The 133 subjects selected for this study were gathered from heavy drinkers whose alcoholic history varied from two to 50 years. They were classified in two groups. The first (75 subjects) was composed of patients admitted for mental manifestations associated with alcoholism. The other group was formed of patients admitted in acute alcoholic intoxication and included 53 men and one woman. Only 10 showed upon admission clinical evidence of hepatic deterioration; of these five had a palpable liver.

The following precautions were taken. (a) The tests were performed at least eight days after admission, in acute cases of intoxication. Experience has shown us that this period of time is quite sufficient to evaluate the *basal* hepatic function. (b) The tests were performed in the fasting state. (c) The patients were maintained in the supine position during the test. (d) All the blood specimens were collected by the same technician, while the residual dye was estimated either by the same person or by one of the authors (G.N.), to assure uniformity of procedure.

Five milligrams of BSP per kg. of body weight was given intravenously and blood samples were collected after 5, 30 and 45 minutes from patients of the first group, and after 5, 10, 15, 30 and 45 minutes for the second group. Every jaundiced or hæmolysed sample was rejected. BSP dye retention was evaluated against a blank formed from the combined specimens of serum for each determination.

The two modifications of the original bromsulphalein excretion test most generally employed consist in the intravenous administration of either 2 or 5 mgm. of dye per kg. body weight, and the subsequent estimation of the residual dye at regular intervals, usually varying from five to 45 minutes. These conventional methods pre-suppose that two individuals receiving the same dose per kg. body weight have an identical dye concentration in the plasma at the start of the test. This is rather inaccurate. Individuals with the same body weight may have varying plasma volumes. A more quantitative method is therefore needed to evaluate the removal of BSP in the body. This modification of the test is known as BSP clearance. Bromsulphalein disappearance is exponential. By plotting the concentrations of dye (or retention percentages) against time on semi-log graph paper (Fig. 1), it has been observed that subjects with good liver function show a rapid fall which continues until all the dye has disappeared, while if function is poor, there is a flattening of the curve or decrease in the rate of removal, starting at approxi-

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mately 15 to 20 minutes (with the 5-mgm. dose) and continuing until all the dye has disappeared.[6]

The BSP clearance may be measured quantitatively when dye concentration at different intervals is known, together with the plasma volume. This value is expressed in ml. of plasma cleared per minute per kg. body weight.[7] However a much simpler numerical result of the test may be obtained by evaluating the slope of the curve between definite intervals. Such value is known as the *clearance coefficient*, K. Since the dye concentration at any time is proportional to the percentage of retention, we have used this last value to approximate this clearance coefficient:

$$K: \frac{\log R_1 - \log R_2}{30 - 15}$$

where R_1 and R_2 equal the percentages of residual dye after 15 and 30 minutes respectively. The value of K may also be illustrated by plotting these data on semi-log graph paper (Fig. 1). The value of this modification

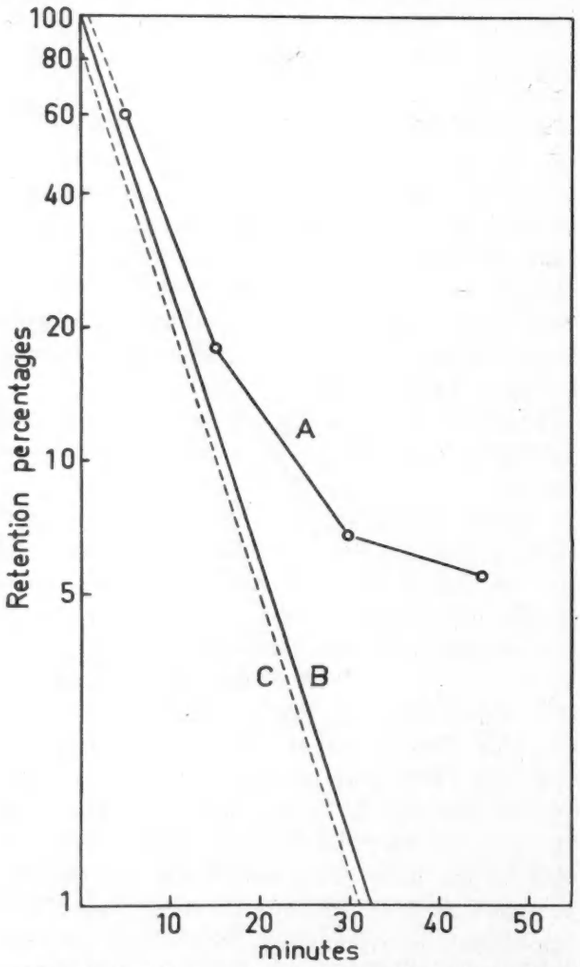

Fig. 1.—Semi-log graph of BSP residual dye in blood in chronic alcoholics (A) and in normal subjects (B).

has been discussed elsewhere.[8] Its main advantage is in eliminating the error of dilution of the dye at the start of the test. It may be assumed that, between certain limits, the value of K is independent of the initial concentration (compare curves B and C in Fig. 1). The rate of removal being identical in both curves, the slope is also identical.

RESULTS

Thirty-eight of the 75 patients (51%) forming the first group retained more than 5% after 30 minutes, the mean retention being 9%. All showed some retention after 45 minutes (mean: 5%) (Table I). In the second group, this abnormality was observed in 56% of the individuals, the mean retention percentage being 7% (Table II). All showed some retention after 45 minutes (mean: 5%). These data agree with our previous observation[1] that approximately 50% of our alcoholics have abnormal BSP retention.

TABLE I.

BROMSULPHALEIN RETENTION PERCENTAGES IN 75 CHRONIC ALCOHOLICS

Obs.	*5 min.*	*30 min.*	*Obs.*	*5 min.*	*30 min.*	*45 min.*
46	59.8	2.4	90	67.0	8.5	5.0
49	62.8	4.2	91	75.5	5.7	——
50	40.5	1.0	92	57.3	2.3	——
51	69.5	22.0	93	80.0	39.6	——
52	59.5	2.7	94	71.0	7.5	——
53	54.5	4.0	95	53.4	5.2	——
55	43.3	5.8	96	74.0	9.4	——
56	51.5	1.7	97	37.0	4.2	1.4
58	49.5	4.5	98	56.0	0.0	0.0
59	88.0	34.0	100	60.8	2.6	——
60	63.0	4.3	101	76.0	22.0	——
61	100 0	34.5	102	59.2	1.3	——
62	59.0	2.0	103	53.0	3.4	——
63	47.5	1.7	104	70.5	9.5	——
64	54.5	4.4	105	77.5	5.3	——
65	56.5	2.0	106	53.0	7.8	——
66	54.5	8.0	113	84.0	15.0	10.8
67	66.2	8.7	114	66.4	4.0	1.1
68	69.0	8.5	115	47.0	——	5.5
69	53.0	5.0	116	47.5	6.0	——
70	39.5	3 5	123	53.2	3.2	2.4
71	50.2	10.2	126	95.0	28.0	——
72	60.0	8.2	128	68.7	6.2	——
74	51.0	2.8	131	80.0	67.0	52.0
75	27.0	2.0	135	52.5	5.3	——
77	54.0	4.7	140	58.7	5.7	3.0
78	76.0	6.0	148	98.0	21.5	14.5
79	52.3	2.5	149	——	17.5	7.5
80	77.5	16.0	153	50.8	——	1.8
81	57.0	3.0	155	57.5	3.0	2.0
82	25.0	0.7	156	66.0	4.5	1.1
83	51.5	6.0	161	40.0	3.5	1.3
84	74.8	9.8	162	63.5	4.5	——
85	59.0	7.5	174	52.2	5.8	2.7
86	45.5	5.0	177	51.0	5.0	2.7
87	——	6.0	179	100 0	23.0	14.0
88	64.0	——	181	89.0	21.5	18.5
89	68.0	6.0				
			Mean:	——	9.0	5.4

Obs.	*Daily lipotrope (tablets)*	*Interval between tests (weeks)*	*BSP clearance coefficient*		
			First	*Last*	*Improvement*
124	3	4	0.025	0.032	0.007
127	12	8	0.025	0.042	0.017
130	No treatment	30	0.024	0.017	−0.007
145	6 (4 weeks)	12 (re-admitted)	0.017	0.029	0.012
146	6	7	0.029	0.034	0.005
151	3 (irregular)	7	0.034	0.032	−0.002
163	6	5	0.033	0.039	0 006
164	No treatment	17 (re-admitted)	0.022	0.020	−0.002
167	6	4	0.016	0 023	0.007
179	6	3	0.016	0.037	0.021
187	10	5	0.015	0.015	0[1]
192	6	4	0.018	0.033	0.015
194	6	4	0.020	0.025	0.005
201	6	4	0.019	0.026	0.007
212	4	5	0.028	0.041	0.013

[1]Cirrhosis.

Table II gives the clearance coefficient K, calculated in the interval between 15 and 30 minutes. In the 54 alcoholics studied for this purpose, K values ranged from 0.006 to 0.049. Forty-five (85%) had a K value inferior to 0.037, the so-called inferior normal limit. The mean K value for the group was 0.028. Ten normal, non-alcoholic controls had K values ranging from 0.045 to 0.077.

Lavers *et al.*[6] have found that the K value (calculated in the interval between 20 and 30 minutes) was inferior to 0.037 in their patients with known liver damage, while 90% of the normal controls had higher values, the mean being 0.082. Goodman[7] has recently reported similar data, from 0.057 to 0.084 in normal controls (mean: 0.067) and from 0.010 to 0.038 in patients with liver disease (mean: 0.022). From comparison of our results with these data, it would appear that the presence of liver dysfunction in chronic alcoholics is emphasized when the BSP clearance method is used.

TABLE II.

BROMSULPHALEIN RETENTION PERCENTAGES AND CLEARANCE COEFFICIENTS IN 54 CHRONIC ALCOHOLICS

Obs.	*5 min.*	*10 min.*	*15 min.*	*30 min.*	*45 min.*	*K-15-30 min.*
73a	90.0	67.5	49.5	15.8	10.8	0.033
76	93.0	60.5	33.0	14.5	9.7	0.024
99a	70.8	33.5	13.3	7.8	7.3	0.015
107	79.0	54.0	38.0	15.0	8.5	0.027
108	74.9	47.9	32.1	11.6	8.6	0.029
109	39.3	19.5	7.5	3.5	2.5	0.022
110	55.5	29.0	15.4	5.4	4.9	0.030
111	58.5	——	10.8	4.0	——	0.029
112	54.3	33.1	21.8	8.5	4.8	0.027
116	47.5	24.5	——	6.0	——	——
117	43.4	22.4	10.2	3.9	2.1	0.028
118	54.5	27.5	——	3.0	2.5	——
119	60.4	33.4	15.4	6.3	4.6	0.026
120	60.0	——	12.8	5.8	5.0	0.023
121	53.5	19.5	8.5	4.3	3.3	0.020
122	66.7	25.2	7.6	1.4	1.2	0.049
124	46.0	24.0	10.3	4.4	4.2	0.025
125	64.2	30.2	14.7	6.2	4.4	0.024
127	83.2	43.2	22.2	9.4	5.4	0.025
129	60.5	29.0	——	5.8	4.0	——
130	51.0	24.2	11.3	5.0	4.3	0.024
132	64.2	30.7	12.2	6.7	6.2	0.017
133	66.3	35.3	17.5	4.5	2.5	0.039
134	64.7	37.2	19.0	6.3	3.8	0.032
136	48.5	23.5	11.5	5.3	4.7	0.022
137	50.5	23.5	11.9	7.3	4.0	0.014
138	54.5	28.3	14.5	5.5	4.0	0.028
139	59.5	32.0	18.0	6.3	5.5	0.030
145	73.8	54.8	42.3	23.8	20.5	0.017
146	70.0	36.7	18.7	5.0	3.7	0.038
147	53.8	——	8.8	4.3	2.8	0.021
150	71.5	32.5	18.5	4.0	2.0	0.044
141	31.0	12.4	5.0	1.8	——	0.030
151	73.8	——	44.8	12.0	——	0.034
152	55.5	——	12.2	4.0	3.0	0.032
157	56.5	23.5	9.5	——	4.0	——
158	60.0	29.3	13.3	5.8	4.4	0.024
159	51.7	22.5	9.7	4.2	3.3	0.024
144	70.8	35.8	23.3	5.3	4.0	0.043
143	48.0	24.2	11.3	3.0	2.0	0.038
160	50.8	23.1	12.4	6.0	5.7	0.021
163	55.0	30.5	13.5	4.3	2.3	0.033
164	85.5	56.0	45.2	21.2	12.0	0.022
165	69.7	38.2	25.4	8.0	4.4	0.033
166	59.5	25.5	14.0	4.7	3.5	0.032
167	72.5	——	30.5	13.5	11.5	0.023
168	88.0	——	28.4	8.6	4.1	0.035
169	64.0	31.0	16.0	4.6	3.8	0.036
170	51.2	——	12.4	3.2	1.2	0.039
171	39.5	23.5	10.5	4.5	4.0	0.024
172	37.3	24.3	10.8	2.3	1.0	0.045
173	40.0	17.0	10.0	7.0	5.0	0.010
175	64.0	——	26.5	6.5	5.2	0.041
176	61.5	26.5	13.5	——	1.5	——
178	70.0	——	31.0	13.0	11.3	0.025
180	54.0	24.0	11.0	9.0	8.5	0.006
182	77.5	——	25.5	8.5	6.0	0.032
183	51.2	23.0	9.0	3.4	2.0	0.028
184	51.5	——	23.5	8.0	7.3	0.031
Mean:	60.6	32.0	18.3	7.0	4.9	0.028

COROLLARY

Most persons involved in clinical work would be inclined to believe that the severity of liver dysfunction is dependent upon the length of alcoholic history. Actually this could not be confirmed by Voegtlin and his associates[9] and no such correlation was observed in our patients. Age seems also to be of secondary importance. However our available data would indicate that the type of beverages consumed plays an important role in this hepatic deterioration. Decreased liver function in our patients is grossly related to beverages in the following order: ale and/or gin, ale and/or whiskeys (rye and Scotch), indiscriminate drinking (including whiskeys, wines and liqueurs). In previous papers,[1, 10] we have stressed the probable toxic action of substances accompanying alcohol in current beverages. Our present data appear to confirm the hypothesis that the liver is called upon to free the organism from these deleterious compounds, along with the alcohol.

SUMMARY

The bromsulphalein test has been found the most useful index of liver dysfunction in chronic alcoholics. More than half of the 178 patients investigated to date showed an abnormal dye retention with the standard 5-mgm. per kg. method.

Since conventional BSP techniques do not allow for individual discrepancies in plasma volume, a modification of the BSP clearance has been used. It has emphasized the presence of liver dysfunction in alcoholics (85%).

It appears that there is a closer dependence of the severity of liver dysfunction on the type of beverages consumed than on age or length of alcoholic history.

PART I

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PART II.—TREATMENT OF LIVER DYSFUNCTION WITH LIPOTROPIC FACTORS

The first signs of hepatic failure in chronic alcoholics appear to be closely related to a progressive deposition of fat in the liver. This fatty infiltration may lead to necrosis and fibrosis (cirrhosis) in extreme cases. There is also experimental evidence that the first phase of this deterioration is for a long while reversible.[1, 2, 3]

Medical science is indebted to Best and his colleagues for having demonstrated that the accumulation of fat in the liver may be due to a deficiency in certain essential factors which are responsible for the turnover of lipids and, accordingly, have been qualified as lipotropic. Choline, for instance, increases the rate of synthesis of liver fat into phospholipids, in which form it is conveyed to the adipose tissue. The body is further able to synthesize choline from methionine, an amino acid found in high protein food. As for cystine, its function appears rather to be antinecrotic.[2]

The hypothesis of a direct toxic action of alcohol on the liver is becoming less and less probable, from which it cannot be concluded however that alcoholic beverages are innocuous. On the other hand, alcohol, because of its high caloric value, may be readily used as a substitute for other foods. This is frequently observed in alcoholics. Alcohol would therefore alter the liver by the intermediary of a secondary nutritional deficiency. Whatever the mechanism involved, when the intake of lipotropic factors is deficient, fat is rapidly deposited in the liver.[4]

Treatment of fatty infiltration of the human liver by lipotropic factors is still in the experimental stage. It is probable that, in many cases, deficiencies in choline or in other factors may be checked by an adequate diet, without the need for therapeutic measures.[5, 6] The procedure, however, will surely vary with the type of patient under observation. Experience has shown us that proper diet is often unattainable, either because the patient suffers from transient intolerance to food or lack of appetite, or because his daily routine is inconsistent with the suggested diet (salesmen and snack bar attendants, river pilots, labourers, railwaymen and their lunch boxes, are examples gathered from our cases). This would also include the so-called "white-collar" group, whose income is inadequate to furnish more than minimal dietary requirements. Therefore, in accordance with other investigators,[4, 7, 8] we used early and intensive therapy to cope with the lipotropic deficiency, the results of which are self-evident.

When a patient is admitted to hospital in acute alcoholic intoxication, a BSP (bromsulphalein) test is prescribed at least eight days after admission. Experience has shown us that this period is quite sufficient to evaluate *basal* hepatic detoxifying function. When there is evidence of liver dysfunction,[9] and in such cases only, Lipotrope* is prescribed, acording to individual tolerance (6 to 12 tablets daily). BSP tests are repeated every three weeks or so, until liver function becomes normal. As pointed out by other investigators, there seems to be no need to remove fats from the diet.

The connection between the BSP test and fatty infiltration of the liver appears to be a close one.[10] Popper and Schaffner[11] report that BSP retention, together with slight hyperbilirubinæmia, may well be the only functional evidence of this type of fatty degeneration. Its use as an objective prognostic index seems well justified.

Forty-eight of our patients were given lipotropic therapy. They all came from social levels that could be qualified as "upper middle" or "middle". In no case was there any suspicion of severe malnutrition due to indigence. Dietary deficiencies, if any, could only be consequent on sporadic substitutions of alcohol for food. In every instance where control tests were possible, there was significant improvement of liver function. Table I illustrates improvements as shown by the rise in BSP clearance coefficient[9, 12] towards normal values. An intensive five-week treatment in one case of cirrhosis (obs. 187) failed to improve liver function, as indicated by the BSP test. This case is still under observation. Controls, on readmission, of patients who re-

*Each tablet contains 500 mgm. of *DL*-methionine, 100 mgm. of choline, 10 mgm. of cystine, 100 mgm. of inositol, 10 mgm. of thiamine, 3 mgm. of riboflavin, 3 mgm. of pyridoxine and 2 mgm. of nicotinamide (Rougier Frères, Montreal).

ceived no treatment (obs. 130 and 164) are included in Table I for purposes of comparison.

Unfortunately, controls are not an easy matter with the type of patients being dealt with and are often obtainable only upon a second admission. Following are four typical observations, the first stressing the lability of liver function in recurrent alcoholism.

Observation 59.—B.D., age 58, has been drinking increasing amounts of alcoholic beverages since the age of 23. He is a heavy drinker and his occupation exposes him to constant overindulgence. On admission, the liver was slightly enlarged. BSP retention was 34% at 30 min., but dropped to 14% in less than a month with lipotropic treatment (8 tablets daily). The patient left hospital without further treatment, but was readmitted exactly one year later to another institution, in acute alcoholic intoxication. BSP retention was now 23%. Treatment was not possible due to lack of co-operation on the part of the patient.

Observation 145.—This patient was a chronic alcoholic (age 39) who has been a regular ale drinker for many years. Clinical examination on admission revealed a conjunctival subicterus. BSP retention, eight days later, was 24 and 20% after 30 and 45 minutes respectively, and the clearance coefficient was as low as 0.017. Following detoxication, the patient was discharged from hospital and, for one whole month, took 6 Lipotrope tablets daily. During this time, he refrained from drinking. Then, as he admits readily, he began drinking again (15 to 20 pints of ale daily) for the two following months. A control BSP revealed however some improvement—10 and 6% after 30 and 45 minutes (clearance coefficient; 0.029). On discharge the patient was presented with 200 Lipotrope tablets, but has not reported since.

Observation 101.—This woman (the only one of the group studied), aged 39, belongs to a high social stratum and has been exposed to alcoholic excesses for the last ten years. Her alcoholic diet consisted of whiskeys, liqueurs, etc., in large quantities. The following data (Table III) show the changes in BSP retention on admission and during the course of treatment (9 Lipotrope tablets daily).

TABLE III.

Observation 101	*B.S.P. retention percentages* 5 min.	30 min.	45 min.
On admission	76.0	22.0	—
7th week	47.9	6.6	3.2
13th week	40.0	0.0	0.0

TABLE IV.

Days	*5 min.*	*10 min.*	*15 min.*	*30 min.*	*45 min.*	*K*
1	83.2	43.2	22.2	9.4	5.4	0.025
11	Lipotropic therapy begun.					
25	52.0	24.0	14.5	4.3	3.3	0.035
40	41.8	24.8	15.8	4.6	3.0	0.036
57	52.8	32.6	20.2	4.8	—	0.042

Treatment was discontinued and a repeat BSP test, four months later, gives the same results, namely 34, 0 and 0%.

Observation 127.—Over a period of 20 years, this patient has drunk "several" bottles of ale daily. On admission, he showed Korsakoff's syndrome, without gastrointestinal or hepatic symptoms. BSP retention however was grossly abnormal (Table IV). For two months, the patient received 12 Lipotropes daily. Table IV gives the BSP values during treatment.

This case illustrates the superiority of BSP clearance over retention percentages in the evaluation of treatment.

SUMMARY

A group of alcoholic patients, with abnormal liver function, was treated successfully with lipotropic factors (including choline, methionine and inositol). Although it has been demonstrated that a proper diet may cope with a fatty liver, the addition of lipotropic factors to ordinary diet may be indicated in patients who, for various reasons, cannot eat properly.

The authors wish to express their thanks to Drs. L. Patry and D. Bédard, from the Clinique Roy-Rousseau, to Drs. H. Nadeau and G. Drouin, from the Hôpital du Saint-Sacrement, and to Dr. M. Bouchard, from the Hôpital Saint-Michel-Archange, for their valued collaboration, as well as to Mlle M. Lizotte, who has shared the technical responsibility of this work.

PART II

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NEONATAL MORTALITY

The death rate of the newborn infant, largely determined by prematurity, is today our number one public health problem. Few people realize that the death rate of an infant less than one day old is more than 6,000 times that of a ten-year-old school child! From the point of view of our national economy the problem is of far greater importance than that of heart disease or cancer, both of which had been widely publicized. In round numbers, infant deaths in the United States amount to one million annually as compared to two million for cancer and four million for heart disease. But if one considers the fact that an infant saved has an expectancy of 38 years of productive life as compared to five years for the cancer patient and four years for the patient with heart disease, it is apparent that wastage of infant life involves a considerably greater man-power loss than do heart disease and cancer combined. The problem can be successfully attacked, and by the same tools!—Conference on Prematurity, Congenital Malformation and Birth Injury.

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THE ABSENCE OF EFFECT OF CORTISONE THERAPY UPON PLASMA LIPID LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS*

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THE OBSERVATION of Philip Hench and associates[17] at the Mayo Clinic that symptoms of rheumatoid arthritis frequently showed remission during pregnancy and jaundice, prompted a trial in 1948 of Kendall's cortisone as synthesized by Sarett of Merck. The dramatic results, temporary though they may be, are now well known. The reported clinical observations of Hench raised in our minds the possibility that cortisone might influence the level of plasma lipids and that there might be some relation between this effect and the action of cortisone in rheumatoid arthritis. Pregnancy is accompanied by a lipæmia.[8] Liver disease may be accompanied by a lipæmia or a lipopenia[11] or by normal plasma lipid levels.[7] Has cortisone a lipæmic effect or a lipopenic effect, or has it no significant effect upon blood plasma lipid concentrations?

Arrangements were made to investigate this question at Queen's University and the Kingston General Hospital in 1950-1951. The clinical studies were part of a programme of research[21] upon rheumatoid arthritis being conducted on the Medical Services of the Kingston General Hospital. The laboratory investigations were carried out in the Department of Pharmacology at Queen's University. Grants in support of the technical expenses of the investigation were made by the Canadian Arthritis and Rheumatism Society, the Canadian Life Insurance Officers Association and the National Research Council of Canada. A preliminary report of results was presented by one of us (H.G.K.) before the annual meeting of the Canadian Rheumatism Association, held in conjunction with the 83rd annual meeting of the Canadian Medical Association at Banff, Alberta, June 10, 1952.

LITERATURE

At the time this investigation was started, there was little published information upon the question involved but certain data have been reported in the intervening years. The administration of cortisone to animals has been found to produce a lipæmia in some species and to have no effect in others. In rats there is an increase in total, free and esterified cholesterol in serum[32] and lipid phosphorus or phospholipid.[25] A similar response to cortisone[14, 22, 29] or adrenal cortical extract[19] is obtained in the rabbit, together with an increase in lipoproteins of the S$_F$ 10 to 30[14] and 40 to 400[28] classes. Cortisone has been reported to be without influence upon blood lipids of dogs[1] and cockerels.[31]

Variable results have been obtained from administration of cortisone to patients with differing ailments. Conn, Vogel and associates[12, 13] reported a temporary, slight fall in serum cholesterol level and similar results were found by others (for example[15, 23, 27]). On the other hand, Adlersberg, Schafer and associates[2, 3] found the serum cholesterol fractions and phospholipid increased by one-fifth and neutral fat decreased by two-fifths in 18 patients with various diseases. The administration of cortisone to patients with rheumatoid arthritis has been reported[6, 20] to have no significant effect upon the serum concentration of cholesterol.

We were not concerned primarily with corticotropin in this investigation. It may be noted in passing that corticotropin has been reported to have a lipopenic effect,[13] a slightly lipæmic effect,[2] and little or no effect except in patients with marked nephrotic lipæmia.[30]

PLASMA LIPIDS IN RHEUMATOID ARTHRITIS

Since our interest in this investigation was in the effect of cortisone upon plasma lipid levels in patients with rheumatoid arthritis, it was considered desirable to establish the concentration of plasma lipids in this disease as determined by Boyd's modifications of the oxidative micromethods of Bloor.[9] A summary of the results obtained upon 43 such patients, compared with corresponding values in 16 healthy, normal young adults (interns at the Kingston General Hospital and research associates in the Department of Pharmacology at Queen's University), is presented in Table I. The range of concentrations of lipids in blood plasma of patients with rheumatoid arthritis was found to be no different from that of healthy, normal adults. A possible exception was plasma phospholipid. The levels

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of phospholipid averaged 25 mgm. per 100 ml. of plasma less in patients with rheumatoid arthritis, the mean difference having a standard error of 9 and hence a P value of 0.01 as calculated after Bradford Hill.[18] While the concentrations of plasma lipids alter slightly with age, the normal values given in Table I are very similar to those

TABLE I.

THE LIPID COMPOSITION OF BLOOD PLASMA IN PATIENTS WITH RHEUMATOID ARTHRITIS. (VALUES FOR LIPIDS ARE EXPRESSED AS MGM. PER 100 ML. OF BLOOD PLASMA).

Lipid	*Calculation*	*16 normal persons*	*43 patients with rheumatoid arthritis*
Total Lipid..	Mean	506	516
	Standard deviation	34	119
Neutral fat..	Mean	125	163
	Standard deviation	58	64
Total Fatty acids.....	Mean	295	317
	Standard deviation	27	69
Total cholesterol.	Mean	149	143
	Standard deviation	20	34
Ester cholesterol.	Mean	104	99
	Standard deviation	21	28
Free cholesterol.	Mean	45	44
	Standard deviation	8	10
Phospho-lipid.....	Mean	168	143
	Standard deviation	30	33

of a larger group of 118 persons covering a range of ages analysed by the same technique some years ago.[10] These results correspond essentially to those previously published. Most previous work has been done upon blood cholesterol which has been found usually normal[4, 5, 26] slightly increased[24] or slightly decreased.[16]

CORTISONE THERAPY

The plasma lipid levels were followed in 18 cases of rheumatoid arthritis during cortisone therapy. Cortisone was administered orally in doses of 100 to 300 mgm. per day, until the symptoms subsided and then in doses of 25 to 100 mgm. per day. Plasma lipid concentrations were determined before and at intervals of two days or longer or up to 29 days after cortisone therapy was started. The mean plasma lipid levels at two-day intervals for 12 days under cortisone therapy are collected in Table II. There was found to be no statistically significant alteration in the concentration of any plasma lipid during cortisone therapy. In individual patients, upward and downward shifts in lipid levels were encountered but there was no consistent trend. Daily normal variations accounted for some individual shifts.[7] Recovery from fever or anæmia accounted for others.[7]

TABLE II.

THE EFFECT OF CORTISONE THERAPY UPON THE MEAN PLASMA LIPID LEVELS OF PATIENTS WITH RHEUMATOID ARTHRITIS.

(VALUES FOR LIPIDS ARE EXPRESSED AS MGM. PER 100 ML. OF BLOOD PLASMA).

	Days of cortisone therapy						
Analysis	*0*	*2*	*4*	*6*	*8*	*10*	*12*
Number of patients....	18	17	14	15	17	12	10
Total lipid.	491	486	532	555	531	524	577
Neutral fat.	158	147	176	192	169	170	181
Total fatty acids.....	304	298	337	349	327	317	356
Total cholesterol..	133	137	142	150	148	143	154
Ester cholesterol..	91	96	99	106	103	98	105
Free cholesterol..	42	41	43	44	45	45	49
Phos-pholipid....	142	141	154	146	157	143	170

CONCLUSION

The concentration of plasma lipids was found to be essentially normal in 43 patients with rheumatoid arthritis and, in 18 of these, to be unaffected by administration of usual doses of cortisone.

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THOMSON'S SYNDROME*

(Poikiloderma Congenitale)

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THE TITLE poikiloderma congenitale was first applied in 1936 by Sidney Thomson[1] to describe a condition in three girls. This began in infancy, with pinkish tense swellings on the traumatic areas of the face and arms, to be followed by telangiectasia, pigmentation and fine atrophy. These patients in addition showed abnormalities of bone development, particularly the skull.

Thomson felt that these cases deserved a special classification apart from Jacobi's Dermatitis Vascularis Atrophicans, which of all the idiopathic atrophies it most closely resembles.

This paper is a brief survey of six patients who present eruptions which followed very closely the pattern so well described in Thomson's original article. The first two cases occurred in two sisters aged ten and five years of age respectively. These were previously observed by me three years ago, with essentially the same changes noted below, except that there is a diminution in colour changes, and progressive pigmentary change. These children have two sisters and two brothers who are unaffected. There were no associated significant circumstances or pre-natal illness, prior to their delivery which was normal. The parents were third cousins, two generation descendants from forefathers born in Alsace and Lorraine, and appeared to be in excellent health. The mother was short in stature and had prominent frontal bones with short stubby fingers.

*Read at the seventh annual meeting of the Canadian Dermatological Association, held at Devil's Gap Lodge, Kenora, Ont., June 8, 1953.

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CASE 1

Female aged 10 years: the mother stated that this girl was born with a half-dollar-sized pinkish swelling on the buttocks. At three months of age, the colour change commenced on the buttocks, legs and arms. Development of the eyebrows and ears appeared at a later date. The eyebrows never did develop, and hair growth was scant. At two years of age, blisters varying from a small pea to a walnut size or larger, appeared on the hands, arms, feet and legs during the summer months, disappearing in the winter. This persisted for two seasons and has not re-appeared since. Dentition was normal, as was nail growth. The child developed in every other way as an ordinary child, and she has shown herself to be of average intelligence. At the age of four years she began to show visual disturbance in June of that year, and by September she was totally blind. She was then operated on for double cataract, with complete return of vision.

Examination at the age of 7 years.—This child presents a reticulated telangiectatic pattern with an underlying fine atrophy of the skin of the face, and with occasional white spots showing through the centre of the eruption. The same mammillated telangiectatic appearance with intervening grooves of fine atrophy and marked pigmentation was apparent on the buttocks. This extended on to the external aspect of the thighs to involve the knees in a cuff-like manner, and spreading on to the legs, particularly the posterior and lateral aspects. The forearms and hands were also involved with a similar pattern, except that in addition to a fine linear type of irregular shiny atrophy, there was a mottled discoloration interspersed between the telangiectatic vessels.

The hands were short and stubby. No abnormalities of teeth, nails or genitalia were noted. When observed three years later, the only change noted was an accentuation of the pigmenting disturbance and slight lessening of the colour phenomenon. The skin was rougher especially about the elbows and knees: "scrubbing made little difference". The telangiectasia was gradually being replaced by fine atrophy and islands of whiter than normal tissue. Blood Wassermann was negative in both parents and child. Calcium and phosphatase blood studies were negative. Vitamin A content of the blood was 50% of normal. Section of the skin from the buttocks showed an atrophy of the epidermis with an almost complete absence of the rete pegs, and an associated hyperkeratosis. Some pigmentation is noted in the basal layer of cells and the epidermal junction is poorly defined. Increased vascularity is a feature, but no inflammatory cell infiltration. The papillary and sub-papillary strata of the epidermis present a pale staining acellular and reticulated appearance with loss of elastic fibres.

CASE 2

Female, aged 5 years.—A normal birth after non-complicated pregnancy. At the age of 3 to 4 months, the mother noticed the first skin changes, consisting of redness of face, buttocks, legs, arms and hands. It was thought to be a heat rash, but the eruption remained, spreading slightly to the eyebrows and ears. At the age of two years, the skin became sensitive to sunlight, and

many blisters of varying sizes erupted on the hands, feet and face during the summer months, which persisted till the fall. This recurred for two seasons, but much less last summer, and so far no recurrence this year. The child was observed by me three years ago, presenting the typical vermilion-red reticulated telangiectasia, with fine atrophy, and slight pigmentation on cheeks and ears, and a similar involvement of the hands, forearms, lower third of the arms, buttocks and legs. The stature was short with stubby fingers. The facial structure was strikingly that of a congenital luetic, with a prominent frontal bossing, saddle nose and apathetic appearance. Eyebrows and hair were scant. Teeth, nails and genitalia were normal. Sweat gland activity not irregular.

Three years later the appearance was quite similar, except that the pigmentary disturbance had replaced much of the telangiectatic involvement, and there was almost a xerodermatous involvement of the upper arms. Hyperkeratosis of the elbows and knees was developing. Wassermann reaction was negative in parents and child. Calcium and phosphatase blood estimates normal. Vitamin A content was 50% of normal, which may be significant. Radiological studies were essentially normal, except for a thickening and shortening of the phalanges.

More detailed study of these girls was impossible, because of refusal of admission to hospital.

CASE 3

Male aged 4 years.—This boy was a two weeks' premature baby, weight 6 lb. 6 oz., otherwise a normal pregnancy. The eruption commenced at eight months, appearing on the arms and forearms first, and then the legs and finally the face. There was no history of pinkish tense swellings. Bilateral cataracts appeared at the age of two and a half years, and he became totally blind in September 1952, and he was operated upon in February 1953. At present in June 1953, the other eye operation is pending.

At the age of two years, blister formation involving the hands and feet occurred in the summer and cleared in the fall and winter months. These healed leaving no scars, but recurred the following summer. No recurrence so far this year. Although a slow dentition occurred, the teeth show no abnormal changes. The child is small in stature, with stubby hands and fingers. There is little or no eyebrow, and the hair of the scalp is scant. The frontal bones are prominent with a saddle nose. The face exhibits a reticular telangiectatic pattern on cheeks, ears and eyebrows, with a typical shiny fine atrophy, with a similar involvement of the buttocks and external aspects of the thighs and spreading to involve the knees and legs in their full circumference. Pigmentation is slight.

Radiographic studies of the skull, hands and feet, revealed only a shortening and thickening of the phalanges. Blood Wassermann of the parents and child was negative. Again admission to the hospital was refused.

CASES 4 AND 5

These were two brothers aged three and four respectively. The older was a twin. The non-affected twin was taller in height, quite bright but rather high strung. These three children were born of healthy parents. The father traced his ancestry two generations back to a great grandfather in Wyoming. He could not definitely state that he was of German origin. The mother is a first cousin of Case 6. She traced her ancestors back to Alsace and Lorraine.

The typical telangiectasis with a fine atrophy and pigmentation, was noted on the cheeks, ears, forehead, buttocks and extremities. The arms and legs of the younger of the two were particularly striking, in that between the reticulated telangiectasia, there was a dappled appearance signified by islands of whiter than normal skin. Both these children were short in stature with short stubby fingers. Blood Wassermann of parents and children was negative. Calcium and phosphatase tests were negative. Vitamin A blood level was 50% of normal. Sections of the skin from the forearm of the three year old revealed some hyperkeratosis with thinning of the epidermis and flattened rete pegs. Stratum granulosum was prominent and the basal cell layer intact. The superficial corium appeared œdematous, and contained a few scattered chromatophores with old blood pigment. The remainder of the corium showed marked telangiectasis and also fragmentation of the elastic fibres. No inflammatory cells were noted. In the deeper corium one hair follicle and a rare sweat gland were to be seen.

CASE 6

Mr. W. aged 36 years. This man is the son of parents still living and in good health, with no obvious defects other than that the mother is short in stature with small hands. An aunt, aged 61 years on the father's side of the family, residing in New York State, is stated to have a similar involvement of the skin. A picture was produced confirming this statement.

The mother states that her son showed no irregularity in development after a normal birth, till about six months of age, when he developed a discoloration of the face, which was thought to be an eczema. To a lesser degree the buttocks, face, upper arms, forearms and hands became involved, and the hips to only a slight degree. She stated that he was intolerant of heat. Eyebrows never developed, and the hair of the scalp was always sparse, and hair was entirely lacking on the face and extremities. At the age of five years he had developed bilateral cataract, resulting in blindness, for which he was operated on with an excellent result. He married eight years ago, but is childless.

The patient was hospitalized and intensive studies produced the following information: He was of short stature, with small hands and feet, with short stubby fingers. He was co-operative and definitely above normal intelligence. The face presented a beetled appearance of the brow, skin dry and wrinkled, with pigmentation and a tendency to keratosis. There was a faint underlying telangiectasis, and the colour of the face became quite markedly reddened under exercise or exposure to heat. The ears showed a faint telangiectasis with tendency to keratotic areas. The hair of the head was scant as were the eyebrows. The face was beardless, and no hair was noted on the extremities and trunk. Hair was scant on the pubis, axillæ and chest. The large toes were dystrophic. The testicles were infantile in appearance.

The skin of the arms, forearms and hands was dry and pigmented with a faint underlying telangiectasia. Hyperkeratotic patches appeared on elbows, knees and dorsum of the hands, and rather marked on palms and soles. The skin of the legs and thighs was soft and velvety to the touch. On the buttocks there appeared a mottled pigmented irregular area of shiny fine atrophy, and a faintly discernible vascular structure. Blood Wassermann was negative. The blood and differential counts were essentially normal. N.P.N. and blood sugar were within normal limits. The basal metabolic rate was minus 10. Pulse 58. Pick up of radio iodine was 10%, suggesting hypothyroidism. Calcium and phosphatase were normal. Vitamin A blood estimation showed a normal absorption of vitamin A, but with impaired utilization, resulting in prolonged and sustained levels, suggesting a vitamin A deficiency on a metabolic basis: 17-ketosteroids were high. Radiological studies of the skull, pelvis, hands and feet, revealed no variation except for shortening and thickening of the phalanges.

Section of the left forearm shows atrophy, slight hyperkeratosis and pigmentation, with well marked telangiectasis. There is considerable loss of elastic fibres, in the papillary and sub-papillary layers of the corium. No hair follicles or sweat glands are to be found.

This last case in addition to exhibiting the basic features of Thomson's syndrome, presents a curious array of inexplicable findings. Certain

endocrine disturbances are present as indicated by hypothyroidism and elevated 17-ketosteroids, with infantile testicular development and sterility. The almost complete absence of sweat glands and hair follicles with dystrophy of the large toe nails could conceivably place him in the congenital ectodermal group. Failure to utilize vitamin A is probably on a metabolic basis. He exemplifies the more extreme variant, referred to later, from the essential characteristics of the simple syndrome.

DISCUSSION

Rook and Whimster[2] referred to 11 cases up to 1949, with constant and distinctive features which seemed to them to justify the clinical entity termed by Thomson poikiloderma congenitale. They felt, however, that the title was inadequate to describe the more complex aspects included in their case, and suggested the title "Congenital Cutaneous Dystrophy" (Thomson's Type), or simply Thomson's syndrome. Dowling[3] and Parkes Weber had previously objected to the title poikiloderma as inappropriate, not only because it seemed not to be related to Jacobi's disease, and thus added unnecessarily to an already too cumbersome classification but was assuredly a developmental defect which should be expressed in the title. Cole commenting on the first case reported in the United States in 1941 by Hailey and Hailey,[4] felt that their case fitted into the "congenital ectodermal" group.

The inclusion of my cases in the literature would further justify Thomson's poikiloderma congenitale as a clinical entity. I am however, inclined to accept the simple title suggested by Rook and Whimster of Thomson's syndrome, with the appendix poikiloderma congenitale. The descriptive appendix serves to orient the present-day observer, later to be dropped when the syndrome as such is generally accepted. This title would seem to preserve the fundamental features originally described and permit to a limited degree additional features to be added to subsequent reports.

Rothmund[5] in 1868, first published the occurrence of cataract in two families suffering from a skin condition simulating closely "Thomson's Syndrome". The first two of the four members had poikiloderma with bilateral cataract, and in the second, two of the seven had poikiloderma with cataract and two poikiloderma alone. Lutz reported the case of a girl with a similar condition suffering from bilateral cataract referred to in Thomson's original article as probably belonging to his series. This child had definite hypoplasia of the thyroid.

Carleton[6] cites in addition a third family reported by Seefelder in 1935, in which of six children, two had poikiloderma and cataract, one having poikiloderma alone. Bloch[7] in 1928, reported two cases with poikiloderma changes commencing in infancy or early youth, both of whom had bilateral cataracts, but with many and varied manifestations, including, nails, teeth, bone and genitalia, which prompted the title "dyshormonal dermatoses". Carleton further discusses the relationship of Werner's syndrome (scleroderma and cataract) with Rothmund's syndrome, stressing the differential points. Reference is also made to the 46 cases of allergic eczema reported with accompanying cataract. She postulated that these skin diseases associated with juvenile cataract are all recessively inherited.

The five children and one adult herein described have all the features of Thomson's syndrome, namely: development of lesions in early infancy on the traumatic areas of predilection with telangiectasia pigmentation and fine atrophy, scant hair, loss of eyebrows, hyperkeratotic changes and bone deformities. However, the additional features of bilateral cataract, transient phase of sensitivity to sunlight with bullous formation, small stature and stubby fingers and consanguinity, only add to the complexity of the syndrome, or might even place these cases in the realms of Rothmund's syndrome. This would further enhance the assumption of Carleton that we are dealing here with a single complicated syndrome, which may vary from the full-blown complexity described in Bloch's case, progressing through the less severe stages of Rothmund and Seefelder[8] as well as my cases to the simplest form as recorded by Thomson.

An exhaustive analysis of these cases is not possible here. I wish to refer to a few pertinent points, which seem to me to be of some consequence. *Consanguinity* has not been heretofore recorded in Thomson's syndrome. The four families included in this report are inter-related. I must confess that three years have elapsed from the time the first three cases were observed, before information obtained from cross-examina-

tion of the father of the sixth (adult case), brought to light consanguinity. The fact that these families of so-called Pennsylvania Dutch descent were bound by a common bond represented by their religious sect (Mennonites), obviated the ferreting out of the relationship. It is quite possible that if the previously reported cases had been seen, under the same favourable condition, consanguinity might have become apparent. A study of the family tree prior to the migration of the families involved, from Alsace and Lorraine to America, would be of inestimable value, but unfortunately all traces were lost. There seems little doubt, however, that the condition is recessively inherited. A second point of interest is the *familial* tendency predominating in three of the families in this report. This occurred only once in two sisters reported previously.

These case histories would suggest that the formerly reported *sex predilection* in favour of the female can be reduced on a proportionate basis from approximately 4 to 1 to 2 to 1. Future recognition of such cases may well prove that there is no particular sex predilection.

The majority of the case reports described Thomson's syndrome in childhood. Few opportunities have been afforded to follow the trend into adult life. Dowling comments on his case of a female aged 22 years, who illustrated the further changes likely to develop. These consisted of an accentuation of the xerodermatous change and the occurrence of hyperkeratosis simulating senile keratosis. Exposed parts were chiefly affected, the skin dry, harsh and atrophic. The patient of Rook and Whimster, a female aged 34 years developed a squamous cell epithelioma of the right ankle, necessitating the amputation of the limb. Case 1 and to a lesser extent Case 2, in the present series, already are developing hyperkeratotic areas on the knees and elbows. The man aged 36 years presents a typical harsh dry atrophic manifestation of the face, with keratotic change evident on the feet, ears and hands. Word has been received that his 61 year old aunt with the identical affliction has had surgical removal of a growth on the forehead and leg, suggestive of keratosis or early malignancy. A final point of interest is that the two adult cases referred to in this paper are married and childless. All of Rothmund's cases, followed years later by Seefelder, except one with a minimal involvement, were childless. One might therefore predict sterility as well as late development of pre-epitheliomatous change in such cases. Some explanation of the facts to the parents would seem advisable. No treatment has been developed for the syndrome, but as the children grow older, constant vigilance to anticipate later skin malignancy should be kept in mind. Surgical removal of the cataracts has been successful in my cases.

SUMMARY

1. Six cases of Thomson's syndrome (poikiloderma congenitale) are reported, five in children and one adult, whose ancestors have been traced to Alsace and Lorraine.

2. Bilateral cataracts developed at the age of five years in three of the cases. The three others have yet to pass the age of incidence for the onset.

3. Consanguinity was proven in the families involved, and a familial aspect is encountered in three of the families involved.

4. Sex predilection in favour of the female has been reduced with the addition of this series, and may be proved not to exist.

5. The title Thomson's syndrome as suggested would preserve the fundamental features originally described by Sidney Thomson and allow the inclusion of any variants herein described, or subsequently to be reported.

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SILENT POLIOMYELITIS

At a time when poliomyelitis was rare in the area, a four year old child attending a Johannesburg, S. Africa, nursery school died of acute poliomyelitis with bulbar paralysis. Stools were collected from 44 children at the school, as well as the teaching staff, in order to determine the extent of silent infection in the school. Among the children, no less than 28 specimens yielded a result positive on tissue culture for Type III (Leon) poliomyelitis virus, although none of these children had shown clinical signs of the disease. Three of the children continued to excrete virus for seven weeks, which suggests that the custom of isolating poliomyelitis patients for three weeks is unsatisfactory.—H. H. Malherbe: *S.A. Med. J.*, 28: 68, 1954.

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CHRONIC ASTHMA

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THERE ARE FEW of the common maladies of mankind that can be so distressing to the patient and at the same time so perplexing to the medical attendant as recurring attacks of asthma. The term asthma is a loose one and covers a multitude of different conditions, differing in nature as well as in causation; but they all have the same end result, that of a feeling of impending suffocation. In view of this multitude of underlying factors in causation, it is hardly surprising that the number of different recommended modes of treatment should also be legion.

Various methods of approach have had their vogue, each one showing a modicum of success when used by its more enthusiastic advocates. Over-enthusiasm on the part of the few, however invariably leads to scepticism on the part of the many, especially when the results claimed cannot always be duplicated. Then with the advent of scepticism there is a slow return of the method to oblivion, and a new one takes its place.

Asthma should be regarded not so much as a disease, but rather as a "pattern of reaction"; in every case the question should be asked "Why does this patient behave or react in this manner?" There may be many answers to this question, but it is only by careful enquiry and investigation along these lines that there can be any hope of success in alleviating this distressing condition.

FACTORS IN PRODUCTION OF THE ASTHMATIC ATTACK

It is not proposed to discuss those attacks which arise as a result of acute heart failure (cardiac asthma) or those cases of chronic shortness of breath resulting entirely from long-standing emphysema or fibrosis (though these may be serious complicating factors in the chronic asthmatic), but rather to confine the discussion to those cases in which bronchial spasm and stenosis occur—whether alone or complicating an acute or chronic infection of the respiratory apparatus.

Three factors are necessarily present in every asthmatic attack: (1) A suitably susceptible "soil". (2) An exciting factor. (3) A "pattern of reaction".

The soil.—It has been long recognized that the so-called allergies tend to appear more commonly in some families than in others and that the type of allergic behaviour is not necessarily the same in each member of the family, nor even in the same individual at different times. The association of asthma with "hay fever", eczema, urticaria or even with epilepsy in the same person or in different members of the same family has long been recognized. It would seem therefore that heredity probably plays some part in the production of the susceptible soil in many instances.

The use of the term "heredity" unfortunately explains little unless some attempt is made to enquire into the nature of those weaknesses and strengths that are handed down to us from our ancestors. Is it merely a pattern of behaviour that is handed down, or is that behaviour in its turn due to some recognizable structural or organic peculiarity of the individual?

It is well known that the immunity response to antigenic material differs in different individuals. Some produce antibodies in higher titre than others. Is the reticulo-endothelial system then more efficient, or does the difference lie in the efficiency of the pituitary-adrenal mechanism? We know that the behaviour of the tissues in response to injury, whether it be as a result of trauma or inflammation, differs in different individuals, and can be markedly influenced by this hormonal system.

Psychomotor and neuromotor sensitivity may also be an important hereditary characteristic transmitted from parent to offspring. It is generally accepted that the threshold of neuromotor discharge differs from person to person, and that the threshold can be lowered or raised by changes in the blood chemistry or by drugs. During the war, persons who desired to escape military service were able to produce a typical epileptic attack by giving themselves an injection of an analeptic drug. Insulin may also be used to produce a convulsion, while in those whose neuron discharge threshold is low, overbreathing may produce the same result. Not many years ago it was customary to treat epileptics with a diet designed to cause a moderate degree of acidosis, thereby *raising* the threshold for cortical neuromotor discharge.

Many attacks of acute spasmodic asthma—especially those which awaken the patient at night—resemble in some respects an epileptic discharge of the visceral type, particularly in its

mode of onset, its comparatively short duration, its frequency after excitement or dietary excesses, and in the ability of the physician to reduce the number of such attacks by the administration of drugs which raise the threshold of neuromotor discharge—phenobarbitone or Dilantin.

Although various peculiarities inherited from our ancestors must be considered to be of great importance in determining our susceptibility to asthma, there is one *acquired* predisposing factor which must not be overlooked: that of irritation, whether mechanical or infective, of any part of the respiratory or digestive tract—the area of distribution of the vagus nerve which is credited with causing reflex spasm of the bronchial musculature.

The lesion most commonly found in the chronic or recurrent asthmatic subject is a chronic (although frequently mild) infection of the upper air passages, characterized by a red, slightly swollen, granular appearance of the mucous membrane of the nose and pharynx. The bacteria cultured from these surfaces are frequently common organisms of low virulence and wide general distribution. Such bacteria as staphylococcus, *Strep. viridans, M. catarrhalis* and Friedländer's bacillus are the most commonly found organisms. Their role is probably more that of maintaining a mild inflammatory state in a mucous membrane previously more acutely inflamed by some short-term acute process than that of setting up a chronic inflammation *de novo*. Chronic sinus infection is also frequently present, with poor drainage and associated polyps. Lymphatic drainage takes place to the posterior pharyngeal wall, and a streak of red swollen lymphoid tissue may often be seen lying behind the posterior pillars of the fauces on one or both sides. Such a state in an asthmatic subject warrants the most vigorous and painstaking efforts to abolish it, for while it exists, the whole mucous membrane is extremely sensitive to all forms of irritation by foreign substances, dusts, pollens, etc., which cease to cause such irritation when the mucosa has again been rendered healthy. It seems, almost, that the apparent sensitivity of these people to specific materials is more in the nature of a mechanical irritation to an unduly sensitive mucous membrane, rather than a high degree of true specific sensitivity.

The part played by climate is a variable one, and generally speaking seems to depend on various factors, of which the presence of dust or other particles in the atmosphere, and the local humidity seem to be of considerable importance, probably because dust particles act as irritants to a sensitive mucous membrane, while excessive extremes of humidity or dryness lead to corresponding changes in the mucous membrane itself.

The exciting factor.—In those persons in whom the soil has been sufficiently well prepared for the development of asthma, either by their ancestors or by various abnormalities acquired by themselves, many varying factors can precipitate a typical attack. Some of these factors have already been mentioned. They may be considered in the following groups: (1) Infective. (2) "Allergic". (3) Gastro-intestinal. (4) Reflex—psychological and somatic. (5) Neurogenic.

1. *Infective.*—An infection of some part of the respiratory tract is perhaps the most common cause of the acute or chronic asthmatic state, and the asthmatic attack which complicates an acute cold or influenza is well known. A careful examination should be carried out in every case, and such an infection should be suspected where there is undue redness or granulation of the mucosa in any part of the nose, throat or larynx. In the chronic asthmatic, cultures from this area are frequently helpful in determining what organisms are present and whether they are sensitive to any of the antibiotics. Vaccines made from these organisms may sometimes be used to reduce the patient's sensitivity to their toxins. As already mentioned, a person who has such a chronic infection will frequently show sensitivity to any non-specific "dusts" which he may inhale, such dusts or foreign particles however being no longer irritating when the mucous membrane has once more been rendered healthy.

2. *Allergic.*—The term "allergy" has come to be one of the most widely misused expressions in medical and lay literature. It has resulted in the "cult" of the allergist, and has been conveniently used to explain the unknown factor in many disease processes. Because of the passive acceptance of the ever-widening orbit of its influence—often without further question—there has resulted a strange stagnation of progress in popular medical thinking regarding the behaviour of tissues, and of the individual as a whole, in response to injury.

It is doubtful whether true allergy to foreign dust proteins alone plays a great part in the pro-

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duction of most asthmatic attacks, unless the mucous membrane has already been rendered unhealthy and sensitive by acute or chronic infection. When such cases occur, they should be accepted only after the most rigid examination of the patient and the exclusion of other pre-sensitizing factors. True sensitization to bacteria and their toxins appears to be not uncommon as the following case will show:

J.B., aged 42, was seen on account of frequent nocturnal asthmatic attacks. Little of note in the way of infection could be detected in his upper air passages apart from a little granular lymphoid tissue on his posterior pharyngeal wall. Cultures were made, however, and showed staphylococci, *Strep. viridans* and Friedländer's organisms. An autogenous vaccine was made, and within half an hour of his first injection he had a full scale asthmatic attack, the first, he had ever had in the daytime. The reason why his attacks occurred only at night may be the absence of nose-blowing and other "clearing" processes during sleep, (so that bacteria and their toxins could accumulate) combined with the usual low degree of adrenergic stimulation at that time.

The anaphylactoid reaction with the production of bronchial spasm, such as occurs in the guinea-pig on injection of a foreign protein to which it has been sensitized, probably rarely occurs in man in the normal course of events. Foodstuffs are sometimes regarded as being causative factors, but skin tests should be interpreted with caution as most ingested foodstuffs are altered considerably by digestion before their absorption across the mucous membrane barrier.

3. *Gastro-intestinal.*—Attacks of asthma are not uncommon, especially in children, after a heavy meal in the evening, or when the eating habits have resulted in a general gastro-intestinal upset. Possibly vagal irritation plays a part in many such cases, causing reflex bronchial spasm. Vomiting frequently occurs in a child who has much bronchial spasm and secretion, with resulting expulsion of some of the secretion and considerable relief of the symptoms. This "gastro-pulmonary" reflex probably plays as great a part in producing asthma as does the absorption of foreign proteins from the food ingested. For this reason, factors which are liable to induce dyspepsia or the retention of food in the stomach for long periods should be avoided. Such factors include eating unwisely or excessively—especially before retiring at night—and the presence of undue anxiety or excitement after a large meal or at bedtime. Adequate sleep and the avoidance of exhaustion are important factors in excitable or emotional individuals.

4. *Reflex.*—The reflex spasm and secretion occurring in the bronchi as a result of irritation elsewhere in the respiratory apparatus or in the gastro-intestinal tract have already been discussed. These may be regarded as true reflex reactions, with the various branches of the vagus acting as the conducting fibres.

Another, more difficult type of reflex to define or to control is the conditioned reflex, which is a conditioned "pattern of response" to some external stimulus. A classic example of this conditioned reflex is that of a child aged 12 who had come to associate an attack of asthma with the presence of horses, and developed a typical attack when a picture of horses was shown on the cinema screen. On another occasion this same boy developed an attack at night, and on questioning, it was learned that he had been dreaming of horses and awoke with his acute attack. Other cases have been observed in emotional children in whom this pattern of reaction has been well established, where recurring nightmares have caused the child to awake with attacks of asthma. This raises the question as to the part played by fear and by the emotions generally in initiating this type of somatic reflex. Some physicians, indeed, have become so impressed with the psychological factors involved that they refer all their asthma cases to the psychiatrist as a routine measure. Unfortunately, over-enthusiasm in a single direction has frequently been responsible for quite rational and useful methods falling into disrepute.

It is unfortunately true that a "habit", once acquired, is difficult to eliminate—especially when a strong emotion such as fear of suffocation has been the underlying factor in its production. It is partly with this in mind that the Asthma Society in England has, with the help of many prominent medical authorities in this field, published a small booklet describing breathing exercises for the asthmatic patient. This booklet describes exercises designed to develop relaxation of muscles and improved methods of breathing—especially in relation to diaphragmatic and expiratory function. These exercises appear to be of considerable help in combating the asthmatic "pattern of reaction" in younger patients, by giving them a more relaxed habit of breathing.

5. *Neurogenic.*—Very little consideration has been given to the possibility of asthma being caused by "discharges" of electrical potential emanating from nerve cells in the cerebrum or brain stem. Indeed it is not definitely established that asthma is ever due to such causes. However,

since visceral types of epilepsy have been described, it seems reasonable to assume that the bronchi and respiratory muscles might occasionally be involved on a focal basis.

A case considered on this basis was that of a man, M.B., aged 64, who complained of severe sharp attacks of asthma occurring two or three times a day and coming on "out of the blue" at any time, when he was reading, playing cards, working, or just sitting chatting with his friends in the evening. These attacks had occurred for several years. The onset was abrupt and duration rarely more than 10 minutes, after which he would again feel comparatively fit. Neurological examination was negative as was also the blood Kahn reaction. Careful attention had been given to the upper respiratory passages, but the attacks persisted. He was then placed on 1½ grains of Dilantin b.i.d. with complete cessation of his attacks. Unfortunately electroencephalography was not performed on this patient.

A careful enquiry into the history will sometimes suggest a focal neurogenic factor but we should guard against assuming that a good response to Dilantin is necessarily proof that the attack is epileptiform. On the other hand it is known that changes in blood chemistry or fluid balance have a marked effect upon the "threshold of discharge" of nerve cells—low blood calcium, high potassium, diminished CO_2 tension or excessive tissue water retention tending to lower this threshold—especially in those who are predisposed to abnormal nerve discharge impulses.

The pattern of reaction.—Much has already been said regarding this subject. In those who are emotionally unstable and who have once reacted to their environment in an "asthmatic" fashion, a conditioned reflex may be readily produced. The more frequently the patient reacts in this way, the more difficult does it become to break him of his habit. Fear of suffocation and of consequent disintegration can result in increasing panic in one who is emotionally constituted, and the facility of response in an asthmatic manner becomes greater with each succeeding attack. It eventually may assume the nature of a reflex reaction which bears very little relation to the severity of the underlying stimulus.

In the light of our experience with the distressing complaint and in view of its complexity in origin and behaviour, no effort should be spared in investigating every case from every possible angle. A careful enquiry should always be made into the circumstances of the first attack, the frequency, duration, and the most common time of occurrence of present attacks, and the effect upon them of changes in climate, residence or altitude, and any ideas the patient himself may have regarding their causation. Enquiry into familial tendencies is also important, especially regarding similar attacks or *related* hypersensitivity reactions.

This should be followed by a minute and critical examination of the upper and lower respiratory tracts, and if necessary the taking of cultures from the nasopharynx and sputum. Psychological and neurological investigation should be considered. Skin tests may be helpful but their importance should not be overestimated and the results should be accepted with considerable reserve.

It is not intended at this time to discuss the emergency treatment of the acute attack of asthma. The long-term treatment of the patient may be briefly mentioned under the following headings: (1) Mitigation of predisposing causes, particularly in relation to environmental factors and familial tendencies. (2) Removal of any discoverable exciting cause, such as acute or chronic infection, sources of allergy, or nasal polyps. (3) Diminishing the effects of the excessive immunity response by means of vaccines, specific or non-specific, or by the short term use of ACTH or cortisone. (4) Attempts to alter the pattern of reaction by teaching relaxation, special breathing exercises, and by the occasional use of psychotherapy. (5) In a few instances it may be helpful to try to raise the threshold of cortical neuron discharge by the use of Dilantin or barbiturates, or by various efforts to change the electrolyte balance. Whatever is done in the way of treatment requires great patience, persistence and ingenuity—frequently in greater measure than many of us are inclined to give. Success, however, when it is achieved, is most gratifying alike to patient and to physician, and depends upon the physician perpetually enquiring "why does the patient react in this way?"

SUMMARY

Some of the underlying factors in the causation of chronic asthma are discussed, as well as the essential nature of the asthmatic state.

Stress is laid upon the important part played by the presence of chronic infection in increasing the sensitivity of the mucous membrane to non-specific irritants.

Caution is recommended in interpreting the results of skin tests as an indicator of mucous membrane sensitivity.

Lines of investigation and treatment of the chronic or recurrent asthmatic state are suggested.

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MONOCYTIC LEUKÆMIA*

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SINCE RESCHAD and Schilling-Torgau[1] first described monocytic leukæmia and simultaneously established the individuality of the monocyte much has been written on these two subjects. In a by no means exhaustive search of the literature I have found 300 papers on these themes. It might, therefore, be expected that the last word has been said, but the more critically one peruses the literature the more one realizes that certain aspects of the two problems are not yet fully elucidated.

Information regarding the frequency of the entity is relatively meagre. Of 6,066 autopsies performed at the Grant and Cook County hospitals, Levine[2] records a diagnosis of leukæmia in 58 instances. Of these the monocytic type made up 10%, and constituted 17% of all acute leukæmias. However, "stem-cell" leukæmia formed nine of the 58 cases. Doan and Wiseman[3] list 76 cases of all types of leukæmia studied by them over a period of four years, and record the monocytic variety as constituting 16% of these. Watkins and Hall[4] reviewed all cases of monocytic leukæmia of both Naegeli and Schilling types seen at the Mayo Clinic in the decade 1930 - 40, and recorded 23 of the former and six of the latter types—figures which exclude cases of leukæmic reticulo-endothelioses showing no evidence of differentiation of reticular cells to monocytes. Forkner[5] diagnosed monocytic leukæmia in six out of 16 instances of acute leukæmia in adults studied at the Thorndike Laboratory of Boston City Hospital over a period of two years. Rosenthal and Harris,[6] however, found this variety to make up only 2% of 455 cases of leukæmia studied by them at Mount Sinai Hospital and in private practice over 15 years. For my part, I have made personal study of 10 cases and have seen eight others by reference in the course of nine years. During this time I have been impressed by the uncertainty displayed by pathologists and clinicians alike in specifically designating leukæmias of this family. In the total of 18 cases with which I have been acquainted there have been 13 acute and five chronic, and I propose to describe one rather typical case from each group, and then to discuss diagnostic difficulties and controversial points.

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ACUTE MONOCYTIC LEUKÆMIA

M.C., a white male, aged 47 years, was admitted to hospital on August 31, 1949 because of severe epistaxis and frontal headache of sudden onset during the preceding evening. A truck-driver, he had been in perfect health until five weeks prior to the date given, when he developed "influenza" or "severe head-cold". The acute phase of this lasted for a few days, but recovery had never been complete, and he had since experienced unceasing lassitude and unwontedly easy fatigue. He had had the usual childhood illnesses, but otherwise his health had been good. During recent weeks he noticed that his gums bled easily on brushing, and he thought they were somewhat swollen around two carious teeth in his lower jaw. He fancied also that he had lost some weight, and volunteered that he did not look forward to his meals with accustomed zest.

He was a well-built man, but pale and with blood oozing from both nostrils. Pallor was evident not only in the skin but also in the conjunctivæ and oral mucous membrane. The left lower canine and premolar teeth were carious, and the gums were swollen, boggy, and plum-coloured in relation to these teeth. The tonsils were moderately enlarged, and membranous flecks were seen on the right one. Scanty Vincent's organisms were seen in smears from this. Fine and coarse petechiæ were evident in the skin of the trunk and lower limbs. Dubious small lymph nodes were palpable in the neck and axillæ. It was thought that the spleen was just palpable, but hepatomegaly was not found. The remainder of the physical examination was negative, apart from tenderness over the lower sternum.

Investigation showed RBC 2.9 million; Hb 60%; WBC 37,000; platelets 53,000. Differential count showed polymorphonuclears 25%; lymphocytes 7%; monocytes 9%; promonocytes 15%; monoblasts 43%; eosinophils 1%; normoblasts 3/100 WBC. Marrow aspiration smears showed a highly cellular marrow, of which cells of the monocytic series comprised 51% with about one-third of these monoblasts.

Progress.—Deterioration was rapid; petechiæ became more widespread and numerous; the swollen gums ulcerated, bled and became all but necrotic; the urine was repeatedly smoky and positive for blood, and melæna was obvious. The temperature was slightly elevated throughout (99-101° F.). Finally, one week after admission, with his hæmoglobin level down to 23%, he lapsed into coma and died.

Autopsy revealed petechial hæmorrhages in skin, pleuræ, pericardium, and wall of the intestine. The liver was enlarged (2,300 gm.) and uniformly pale. The spleen showed loss of Malpighian corpuscles with a pale-red colour to the cut surface. Deep cervical, axillary and mediastinal lymph nodes were enlarged (up to one cm.), discrete, and greyish-pink in colour. The lymphoid follicles of the large intestine were prominent, and numerous petechiæ were evident in the mucosa. The kidneys showed areas of mottled pallor and petechiæ in the cortices.

Histological examination of the liver showed moderate numbers of monocytoid cells scattered in the sinusoids with heavier periportal accumulations. Differential counts of the latter were attempted and gave: neutrophils 7; lymphocytes 9; eosinophils 4; monocytes 57%; "blast" cells 21%; cells in mitoses 2%. The Kupffer cells, on the whole, appeared enlarged and hyperplastic and many were loosely attached, but their participation in the proliferative process was not obvious. In the spleen, only vestiges of the lymphoid follicles remained and monocytic cells dominated the picture. A light scattering of neutrophil and eosinophil granulocytes was seen here and there.

Hypertrophy and desquamation of many littoral cells were seen. In the lungs some alveolar septal walls were

thickened (up to 100 μ. or more) due to infiltration with leukæmic cells. The architecture of the lymph nodes was completely destroyed and replaced by loosely arranged large polyhedral cells having pale eosinophilic cytoplasm and large irregularly shaped nuclei with delicate chromatin network. Plasma cells, lymphocytes and very occasional granulocytes were lightly scattered among the dominant leukæmic cells. Infiltrations of the characteristic cells were also seen in the renal cortices, while the mucosa and submucosa of the colon showed very loose collections of leukæmic cells often interspersed with hæmorrhage.

CHRONIC MONOCYTIC LEUKÆMIA

F.W., a male clerk, aged 64 years, sought medical advice because of pallor and breathlessness of insidious onset and increasing severity in the course of the antecedent 7 months. During the past two months he had experienced numbness of the fingers with symptoms of intermittent claudication in the preceding six months. Past and family histories were negative. On examination he was seen to be fairly well nourished but very pale. The finger-nails were flattened and brittle. There was no detectable hepatic or splenic enlargement, and no lymph nodes were palpable. A few days later he was referred to me for hæmatological examination and confirmation of a clinical diagnosis of pernicious anæmia. On October 10, 1944, I examined his peripheral blood and found: R.B.C. 1.47 million; Hb 5.4 gm. (37%); W.B.C. 14,200; polymorphonuclears 34%; lymphocytes 29%; eosinophils 2%; monocytes 35%. From this picture I suggested a diagnosis of monocytic leukæmia, and the patient was admitted to hospital on October 20. One pint of whole blood and one pint of concentrated erythrocytes were immediately transfused. The heterophil antibody titre and Wassermann reaction were negative. The platelet count was 61,000 on admission, and fell to 41,000 ten days later; the Hess capillary fragility test was positive. On October 28 smears of sternal marrow aspirate revealed neutrophil granulocytes 17%; neutrophil myelocytes 2%; myeloblasts 1%; eosinophils 6%; lymphocytes 12%; monocytes 55%; early monocytoid cells, 4%; plasma cells 1%; normoblastic nucleated red cells 2%.

Subsequently his white cell count steadily increased, *e.g.*, 46,000 on November 22, with polymorphonuclears 7%; lymphocytes 15%; monocytes 77%; monoblasts 1%; normoblasts 2%. At one time two neutrophil myelocytes per 100 white cells were seen in smears of peripheral blood. The only other findings of note were: (1) On admission his M.C.V. (mean corpuscular volume) was found to be elevated at 109 c.μ.; (2) smears made from fresh heparinized blood incubated at 37° C. for 20 minutes with addition of a few drops of india ink (diluted 1:10 with saline) showed clustering of, and active phagocytosis of, india ink particles by monocytes. This was a very striking phenomenon when observed on the warm microscope stage, when the pseudopodial activity of the monocytic cells could be seen to best advantage.

His condition gradually and progressively weakened, and he died on November 28, *i.e.*, 8 months from the known onset of his disease. At no time were spleen, liver or any lymph nodes palpable, and petechiæ or oral signs never appeared. However, with reference to the latter, it must be stated that the patient was edentulous.

Salient features of autopsy.—There was generalized pallor of the liver, and obfuscation of the lymphoid follicles of the spleen, which was pale. The faucial and lingual tonsils were symmetrically hypertrophied. All the deep cervical lymph nodes were discretely enlarged (up to 1.5 cm.), of soft rubbery consistency and pale greyish-pink colour. There was one pea-sized node in the right axilla; no other nodes were enlarged; the bone marrow of the mid-femur was hyperplastic and pale brownish-red. There were numerous stellate hæmorrhages up to one cm. in diameter in the subarachnoid space and superficial layers of cerebrum over the vertex and left temporal pole.

Histology: Leukæmic monocytoid infiltration of liver, lungs, pelves of kidneys, and spleen; diffuse replacement of lymph nodes with monocytoid cells, mostly of mature type, with occasional interspersion of plasma cells and mononuclear giant cells.

DISCUSSION

From the literature it is apparent that acute is very much more common than chronic monocytic leukæmia. Of 65 reported cases, where adequate details are available, I have found 49 acute and 16 chronic (of more than six months' duration). Osgood[7] found 80 acute cases and 24 subacute or chronic cases in the literature.

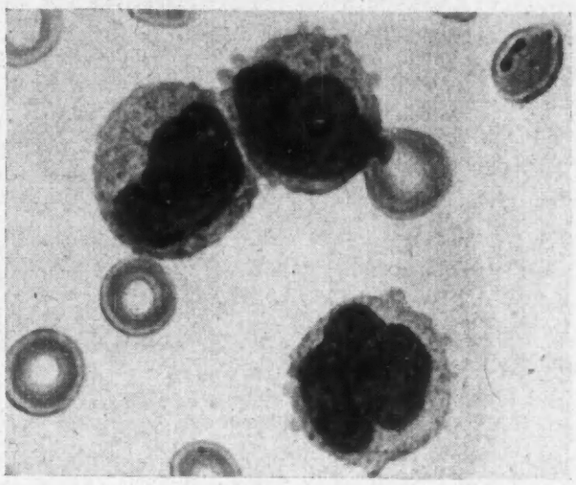

Fig. 1.—Leukæmic monocytes in peripheral blood in case of chronic monocytic leukæmia. (Leishman stain; x 1,600).

In the 49 acute cases which I have found the average age of the patients was 44 years (range 5 to 76); 67% were males; the mean duration of the illness was 10 weeks; the average of the highest white cell counts was 94,000 per c.mm., and the mean of the lowest counts recorded was 17,000. In the 16 chronic instances 75% of the patients were male; the mean age of all 16 was 56 years (range 31 to 71); the average duration of the illness was 21 months (range 7 to 96 months). I myself have seen a case of the chronic type survive for 3½ years from the known onset of his disease. In the 16 recorded cases of this type the mean of the highest white cell counts recorded was 73,000, the average of the lowest being 6,000. Indeed, many of these cases are leukopenic for considerable periods, and I have seen cases run peripheral white cell counts of 4,000 to 6,000 for months, the only abnormal findings being anæmia and an increase in large, mature, convoluted monocytes. Osgood[7] found that 67% of monocytic leukæmias of all types

occurred in males. Of 124 cases in the literature he found 12% in which the white cell count was never elevated, and that counts were consistently elevated in only 52% of cases. He recorded the average duration of 104 cases as 5½ months (range 10 days to four years). Watkins and Hall,[4] in their 29 cases had only 10 acute to 19 subacute or chronic types.

onset. Occasionally, the first sign has been cutaneous infiltration—a not uncommon occurrence, and usually in the form of bluish or purplish-red papules (Sydenstricker and Phinizy;[15] Doan and Wiseman;[3] Forkner[16]), or as an eczematoid or vesicular eruption (Giffin and Watkins[17]). Not infrequently furunculosis has been mentioned (Hart;[18] Osgood;[7] Forkner[5]), and

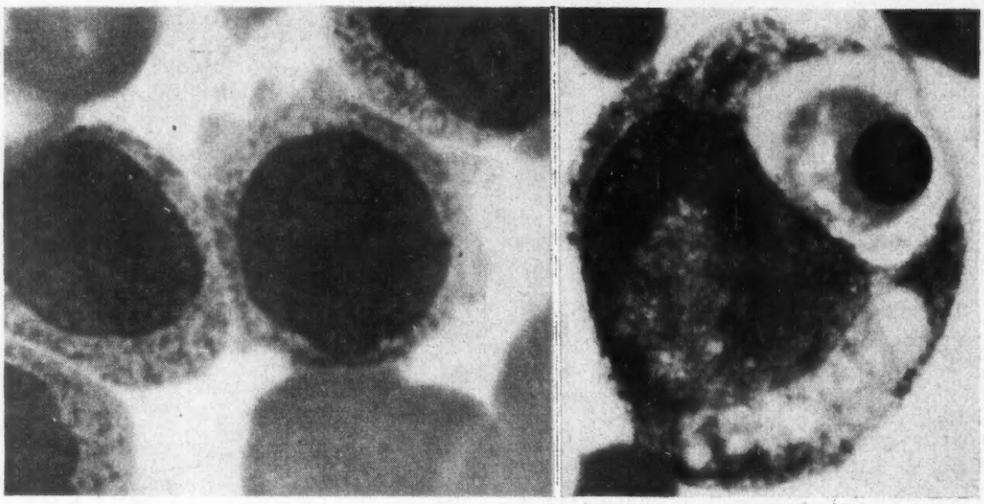

Fig. 2 Fig. 3

Fig. 2.—Promonocytes in peripheral blood in subacute monocytic leukæmia. (Wright's stain; x 3,200). Fig. 3.—Phagocytic giant vacuolated cell in marrow in chronic monocytic leukæmia. (Leishman stain; x 2,000).

Though some authors, *e.g.* Kracke and Garver,[8] Doan and Wiseman,[3] and Whitby and Britton,[9] consider monocytic leukæmia to be indistinguishable clinically from the other leucoses, the consensus is that it possesses a certain degree of individuality. Forkner[5] considered that swelling and ulceration of the gums was characteristic of the acute variety. Osgood[7] found this condition in 80% of 88 recorded cases in which the gums were mentioned. One of the first intimations of disease has come from the dentist's chair in a remarkably large number of cases, *e.g.*, Ewald,[10] Forkner.[5] Often the illness has been dated from an attack of influenza, sore throat, or upper respiratory infection, and severe frontal headache has been a prominent feature in many, *e.g.*, Campbell *et al.*,[11] Reich,[12] Levine,[2] White,[13] Heller and Hiles.[14] Not infrequently the illness has been heralded by nosebleeds, as in one of my own cases, and purpura and ecchymoses are very common in acute cases (69% of 80 cases according to Osgood[7]) and in the acute terminations of the chronic types. Pallor, weakness, and a febrile toxic state are usual in the acute variety, in which anæmia is almost always profound and of rapid drenching night sweats have been recorded (Farrar and Cameron[19]). Not uncommonly, especially in the chronic forms, the onset is insidious with symptoms referable to anæmia (Clough[20]). Indeed, this is probably the commonest mode of onset in the chronic variety: nine of the 16 chronic cases previously mentioned began in this way. This, combined with the age incidence, and with the facts that the anæmia may be macrocytic (second case above), the white cell count often not elevated, or even leukopenic, and glandular, hepatic and splenic enlargement clinically not detectable, necessitates the exclusion of pernicious anæmia from the diagnosis of the chronic form. The combination of the two diseases, *i.e.*, leukanæmia (von Leube[21]), can only be diagnosed by marrow examination.

Lymph nodal enlargement offers a feature of particular interest in monocytic leukæmia. In almost all recorded cases it has been slight; in many it has eluded clinical detection. The cervical group of lymph nodes have chiefly been affected (Forkner[5, 16] and Sydenstricker[15]). Whitby and Britton[9] attribute this to oral sepsis,

but careful analysis of recorded cases shows that this is not so. In 53 reported cases, for which adequate data were available, I have found recorded lymph node enlargement (clinical and autopsy) as follows: cervical, 35; axillary, 22; inguinal, 18; tonsils, 12; peribronchial and mediastinal, 12; para-aortic, 10; mesenteric, 7; supraclavicular, 3; epitrochlear, 3. In 10 cases there was no lymph nodal enlargement at any time. In 8 instances cervical lymph-node enlargement was absent when oral manifestations were noted, while in 20 cases the lymph nodes of the neck were enlarged at a time when no oral sepsis was present. Forkner[22, 23] found that monocytes were produced chiefly in the peripheral lymph nodes in the rabbit. To my knowledge, no comparable study has been made in man, and the above figures may be significant in the light of Forkner's evidence.

Leukæmic infiltration of the alimentary tract is a commonly recurring feature in the literature on monocytic leucosis. It is apparent that alveolar and gingival infiltration have necessitated the common tooth extraction referred to above. Ulcero-necrotic and infiltrative lesions of the ano-rectal region have been recorded by Forkner,[5] Haining, *et al.*;[24] Campbell, *et al.*;[11] and White.[13] Clough's[20] case showed leukæmic infiltration of the mucosa and submucosa of the ileum, and the mucosæ of the cæcum and colon were inflamed and ulcerated. This change was also present in case No. 6 of Doan and Wiseman,[3] and I have seen it on two occasions, and have been impressed with the similarity of lesions seen in Letterer-Siwe's disease.

Enlargement of the spleen and liver is generally slight.[15] Forkner[16] remarked that it was often not clinically detectable, though frequently found at autopsy, but he had previously[5] stated that the spleen was palpable in 70% of acute cases. Osgood[7] noted that hepatomegaly was almost as common as splenomegaly; he found it in 66% of 90 recorded cases.

Of the cytological changes in the organs, Wintrobe[25] noted the relative lightness of the organ infiltrations as compared with other leukæmias. In the liver, though some cases have shown a preponderance of periportal infiltration, in most cases this has been diffuse as in myelogenous leukæmia. Indeed, histopathologists have tended to label these cases myelogenous because of this distribution. Many (*e.g.*, Levine[2]) have inferred, from their hypertrophied, desquamative appearance, that the Kupffer cells have taken part in the proliferative process. Though I have commonly observed this change, I have been unable to attribute to it more than a reactive process. I am not, however, prepared to apply this interpretation to the activity of the splenic littoral cells, and have noted this phenomenon also in Letterer-Siwe disease.

In the spleen many observers have remarked on the presence of appreciable numbers of plasma cells,[1, 7, 10] and these elements have also been noted in the blood.[15, 20] Many, too, have remarked on the presence of plasma cells in the lymph nodes. Eosinophils in small to moderate numbers have been noted occasionally in the spleen and/or lymph nodes.[3, 20] Binuclear, mononuclear, or multinucleated giant cells, the first often not unlike the Sternberg-Reed cell, have frequently been reported in these organs,[2, 5, 20] and occasionally in the marrow.[3] Indeed, the microscopic appearance may at times be vaguely reminiscent of Hodgkin's disease,[26, 27] especially in the spleen. Downey[27] suggests that this similarity is more likely to occur in the Schilling type. In one of my cases, not recorded here, approximately 2% of the marrow cells were giant early or blast monocytoid cells up to 60-70 μ. in diameter, the nucleus often being characteristically folded or indented. The cytoplasm of these cells was of a deep blue colour, occasionally somewhat muddy, and often displayed clear cumulus-like vacuolated areas that began near the *Hof* of the nucleus and spread until they occupied most of the cytoplasm in the more mature of these cells.

Local tumour-like formations of monocytoid cells have been recorded in a number of cases.[28, 29, 30] Alveolar septal thickening due to leukæmic infiltration in the lungs is common.[3, 5, 14, 31] This may be due to local formation of monocytes,[23] though it may more often be attributable to "filtration" of monocytes from the blood.[32, 33]

The cell types in the peripheral blood have been the cause of much controversy and speculation. Commonly, especially in the more chronic forms, the mature monocyte forms the predominant cell. Not uncommonly it is the only cell type to be seen increased in the monocytic cell series, though diligent search will usually reveal an occasional cell which is less mature. The mature (Schilling type) monocyte as seen in these cases is a large cell (15-30 μ.), of somewhat

irregular outline, and often showing marginal pseudopodial cytoplasmic protrusions. The cytoplasm is ground-glass-like, contains few to moderate numbers of fine azure granules (may be agranular), and is frequently vacuolated. The nucleus may be boomerang-shaped, though it is often highly irregular and convoluted (usually more so than that of the monocyte of normal blood) and looks like an aerial view of an undulating mountain chain. Sponginess and a lacy appearance are often striking features.

In the more acute forms, and in the terminal stages of the chronic cases, promonocytes and blast cells are present in varying numbers. The latter in their typical form have a basophilic (blue with Wright's or Leishman's stain) cytoplasm with a tinge of grey, and this is relatively more abundant than that of myeloblasts or lymphoblasts. The nuclear chromatin presents a coarse reticulo-granular appearance. The nucleoli (1-5) are very irregular in size and shape, and the parachromatin is poorly marked, giving them an indistinct outline. Even in the blast stage the tendency to indentation and convolution on the part of the nucleus is usually well shown, and small cytoplasmic pseudopods are often prominent. Especially in the very fulminating acute cases, there are present in the blood and marrow smears blast cells of somewhat different appearance. These display with Romanowsky stains a very muddy greyish-brown cytoplasm having only a tinge of blue. The nuclei are also intensely hyperchromatic, but usually show indentations or actual convolution. The cytoplasm may be studded with fine dark granules, and small cytoplasmic pseudopods are common.

TYPES OF MONOCYTIC LEUKÆMIA

Many acknowledge two types, *viz.* Schilling and Naegeli, but close study of the literature and of personal cases reveals no clear-cut clinical or cyto-histological differences between these allegedly distinct varieties. The confusion is, in part, as Forkner[16, 34] has stated, due to confusion of cell types. Too many authors have attempted to deduce too much from minor details of cytological structure. It is interesting to note that when Schilling-Torgau and Reschad[1] sent the films of their case (without comment) to Naegeli, the latter observed, "The smear contains almost entirely cells of the type of normal transitional forms, and, indeed, in such numbers that one might take it as a transitional cell leukæmia. The latter, however, has not yet been encountered". Later Naegeli[35] set himself strongly against the recognition of monocytic leukæmia as an entity, and proceeded to discredit many reported cases. He believed that monocytes were derived from myeloblasts. Hence it was that Downey[27] gave the designation "Naegeli type" to those cases in which "myelocytes" are present in relatively large numbers. The monocytes in this form are supposedly derived from myeloblasts, whereas in the Schilling variety they derive from reticulo-endothelial cells. It is difficult to conceive of an adult cell being capable of origin from two distinct elements!

Many authors have remarked on the number of cases of monocytic leucoses which have terminated in a "myeloid phase",[8, 12] but Forkner[34] remarks, "The evidence seems insufficient to justify the acceptance of a transformation of one type of leukæmia into another". Undoubtedly, at least a few of these cases have been myelogenous ones in which the myeloid cells have lost their capacity to form granules. Also, that a few normal "irritation" myelocytes may be present in the blood in monocytic leukæmia is accepted by all. However, in many of these supposedly transformed leukæmias the altered diagnosis has been arrived at by histological examination of autopsy material—a relatively unreliable method as compared with study of blood and marrow smears by a competent hæmatologist. For my part, I have found it impossible to convince myself of the existence of the so-called Naegeli type. In the few cases which I have seen conforming to this alleged type the marrow failed to show any increase in myeloblasts; in fact, these elements and their progeny were usually reduced. Close inspection of the cells both of the blood and marrow has in all cases revealed the typical monocytic nuclear convolutions in a high proportion of cells, and the nucleolar and chromatin pattern has been characteristic of the monoblast. Lastly, cytoplasmic pseudopodia have been exceedingly common. Many have fallen into error by paying undue attention to cytoplasmic granules, which may be very scanty or abundant. With Reschad and Schilling-Torgau[1] I am unable to attribute any differentiating value to the oxidase reaction, except perhaps in degree. In any case, Katsunuma[36] demonstrated that the cells of the reticulo-endothelial system are weakly oxidase-positive. Considering this, and the active phagocytic

propensities of the monocytes, it is advisable to exclude the oxidase reaction from the diagnostic armamentarium. By analogy with malignant processes elsewhere, I am led to interpret atypical cells as an expression of degree of neoplasia and de-differentiation. In this connection, it is pertinent to state that the cases which show well matured and differentiated monocytes of the "Schilling" type are unquestionably the chronic ones.

A great deal of the confusion in the literature is due to the lack of agreement on the origin of the monocyte, study of which reveals a succession of hypotheses strewn with the wreckage of speculative theories, of which there have been no less than 19.[16, 35] However, it is abundantly clear that the conclusion of Cunningham, Sabin and Doan,[37] and of Forkner,[22, 23] *i.e.*, that monocytes derive from primitive mesenchyme cells via the monoblast, is the most acceptable. It is clear too, from the work of Sabin,[38, 39] of Sabin, Doan and Cunningham,[40] of Aschoff,[41, 42] and of Forkner[23] that the monocyte is closely related to the macrophage (clasmatocyte, histiocyte, tissue phagocyte, adventitial cell, resting wandering cell, pyrrol cell, rhagiocrine cell or polyblast). It is therefore permissible to speak of monocytic leukæmia as leukæmic reticulo-endotheliosis[43] in the wider sense, though separation of cell types such as blood histiocyte or blood macrophages, would appear to be a superfluous refinement. The emergence of plasma cells in the histological picture conforms to this view, since there is strong evidence[44] that this cell is a derivative or cytological variant of multipotent reticulo-endothelial cells. This concept of a leukæmic reticulosis explains also the dramatic development of profound anæmia in the acute cases, where it may be inferred that differentiation of reticulo-endothelial cells is diverted almost entirely along leukæmic lines, *i.e.*, acute monocytic leukæmia is more closely related than any other type to the so-called "stem-cell leukæmia". On this score occasional deviational side-development into cells resembling other elements may be understandable.

Finally, it is interesting to note here that the earliest literature on Letterer-Siwe's disease has centred around monocytic leukæmia or leukæmic - aleukæmic reticulo - endotheliosis.[45 to 50] Much has been written since the rediscovery of this disease, and there has been a growing tendency to link it with two other entities, *viz.*, eosinophilic granuloma of bone and Hand-Schüller-Christian disease.[51, 52] However, there is much in Letterer-Siwe's disease, including its uniformly malignant nature, to justify its separation from the eosinophilic granuloma. Indeed, the case of Swirtschewskaja,[49] which is now accepted as one of Letterer-Siwe type,[53] did show a leukæmic nature with a large percentage of monocytoid cells in the peripheral blood. I have observed such a leukæmic phase in a case of this disease in which frequent blood smears were personally studied, and feel that such a phase might more often be discovered were accurate and close hæmatological studies more often carried out in cases of Letterer-Siwe's disease. Here also, it may be mentioned that cellular pleomorphism has been noted in organs of cases conforming to the Letterer-Siwe type.[53] That this pleomorphism or aberration has tended to the production of plasma cells and giant cells resembling those of Dorothy Reed-Sternberg makes closer the analogy of this much discussed disease with malignant reticulo-endotheliosis and monocytic leukæmia. This is not to say that similarity means identity, though it may indicate a relationship closer than that postulated for Letterer-Siwe's disease with eosinophilic granuloma of bone.

SUMMARY

Two cases are described as examples of chronic and acute monocytic leukæmia, the clinical and pathological features of which are discussed in the light of published work and personal experience. The difficulties and pitfalls of diagnosis are described.

A kinship (not necessarily close) with Letterer-Siwe's disease is briefly discussed.

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HÆMORRHAGIC NECROSIS INDUCED IN A TRANSPLANTED MALIGNANT TUMOUR BY A BIOLOGICAL FLUID*

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EWING, in his treatise on neoplastic diseases,[1] assumed that there exist within the body defensive reactions against neoplastic growths. He felt that inflammation around the tumoral masses represents the principal defensive measure. In one case reported by McKay,[2] improvement was coincident with the absorption of a pleural exudate. Ewing himself followed up several cases in which patients with chronic ascites survived with malignant tumours for an unusually long time.[1-p. 46] From this it might be inferred that the inflammatory process or its products may be involved in the resistance to neoplastic growth.

A survey of the literature on the formation of antibodies against an animal's own tissues (e.g. kidney, pancreas, spleen) led Ewing also to postulate a second mechanism in the sense that: "These observations further support the view that a human tumour-bearing subject may to some extent be immunized by injections of his own tumour tissue."[1-p. 145] So far as the author knows, no attempts have been made to use McKay's observation on the beneficial effect of exudates in therapeutic trials. On the other hand, efforts to immunize tumour-bearing human beings by injections of their own neoplastic tissue are numerous, though disconcertingly negative.

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More recently, Stewart[3] reported well-controlled new cases of "spontaneous regression" of neoplastic disease in man. Direct damage to tumour tissue was induced with subsequent resorption of necrotic or necrobiotic parts. This was accompanied by severe systemic reactions, followed by regression of the neoplasms. The whole picture was very similar to that caused by therapy with Coley's toxins.[4] It is noteworthy in this connection that incomplete surgical removal may lead to the disappearance of disseminated tumours. Stewart, analysing his case and others in which the mechanism of regression was perhaps fundamentally different (e.g. "spontaneous maturation" of neuroblastomas, "dependent and independent growths," "conditioned and autonomous neoplasms," "late metastases" etc.), went so far as to conclude that: ". . . the cancer cell, though superficially anarchical, is not, nor can it be unbiological, just so long as it is part of a biological host."

The problem of the natural defenses against cancers is summarized by Gellhorn[5] as follows:

> "The evidence for inherent defense mechanisms against human cancer is tenuous and yet, on occasion, very persuasive. Thus, the rare but well documented cases of disseminated tumours which spontaneously regress or the less infrequent instances of recurrent cancer many years after removal of the primary tumour suggest that there may be physiological mechanisms which can either destroy malignant cells or hold them in check for long periods."

The experiments reported below were designed to test the possibility that, under particular conditions, a malignant growth may cause self-limiting reactions within the animal's body.

GROWTH OF WALKER TUMOUR IN ARTIFICIAL AIR-POUCH

Zahl and Nowak[6] reported that local tissue injury facilitates the growth of transplanted sarcoma 180 in mice. They also noted that the growth tends to be spherical and a hæmorrhagic liquid accumulates inside the tumoral mass, if the inoculum is placed in a large subcutaneous wound. We approached a related problem with a modification of the artificial subcutaneous air-pouch, as used for the study of inflammation in the so-called "granuloma-pouch technique."[7, 8]

Material and methods: 60 female Sprague-Dawley rats, weighing 160 to 190 gm., were shaved on the back—with clippers—and then 25 c.c. of air was injected with a 22-gauge hypodermic needle into the loose subcutaneous connective tissue. Without withdrawing the needle, 0.5 c.c. of Walker tumour suspension was injected into this air-space under aseptic conditions. The suspension was prepared by grinding Walker tumour with an equal volume of physiological saline solution, adding 800 I.U. water-soluble penicillin per c.c. This technique will be called in this paper the "tumour-pouch technique." As in all experiments reported here, the animals received Purina Fox Chow and water *ad libitum*.

Results.—Within ten days an ellipsoidal neoplastic mass had developed, the lumen of which contained a large quantity of hæmorrhagic, odourless liquid. Without its fluid contents the tumour weighed 30 to 45 gm. and contained from 20 to 65 c.c. of liquid, as well as some clots. The majority of the animals died, in an emaciated state, between the 14th and the 20th day after tumour implantation. Several animals survived up to 48 days with enormous but stationary tumours weighing 60 to 80 gm., not counting the liquid. A high percentage of the animals living longer than 25 days developed pulmonary metastases.

In all animals, which died spontaneously or were killed 12 days or more after implantation, the inner surface of the tumour was covered with a continuous layer of necrotic tissue. The depth of this layer did not depend on the thickness of healthy tumoral tissue. In some sites, the Walker tumour was reduced to a few cells covered inside by a thick layer of necrotic tumour.

We consider it unlikely that the necrosis was due exclusively to an insufficiency of blood-supply. It must be noted that even thin layers of tumoral tissue underwent degeneration with necrosis under these conditions, and small masses of Walker tumour notoriously take very well when inoculated into healthy tissue, although they have no vascular supply at the onset of their growth. Hence, it is reasonable to assume that the hæmorrhagic liquid inside the tumoral pouch played some part in the causation of the necrosis.

Remembering Ewing's statement on the cancer-inhibiting effects of tumoral exudates and liquids, we thought that the pouch-fluid might be the principal cause of tumour necrosis in our experiments. It is noteworthy that in several animals the growth of the Walker tumour in our air-pouch became stationary by the 12th to 14th day after implantation (judged by measurements of its dimensions *in vivo*). However, after withdrawal of the liquid at this time, a sudden increase in growth-rate was noted.

In other experiments, we observed[9] that in the tumour pouch hæmolytic antibodies against intravenously injected sheep erythrocytes accumulate in almost the same concentration as in the blood of control animals without tumours. Consequently the antibodies can be extracted in relatively large quantities from the tumour-pouch liquid.

The following experiments were then undertaken to determine whether tumour-pouch liquid has any tumour-inhibiting properties.

HÆMORRHAGIC NECROSIS IN WALKER TUMOUR FOLLOWING THE INJECTION OF TUMOUR-POUCH LIQUID

Material and methods.—The liquid was prepared as follows. In 80 female Sprague-Dawley rats, weighing 170 to 200 gm., the Walker tumour was implanted by the tumour-pouch technique, as in the previous experiment. On the 12th day, the tumour-pouch liquid was withdrawn with a 15-gauge needle, and 0.1 mgm. of heparin per c.c. was added to prevent coagulation. The liquid was used immediately after this for the first injection, but was then stored in a sealed container at 0-4° C. for further use during the three following days.

Another 80 female rats from the Sprague-Dawley farm, mean body weight 190 gm., were implanted in both legs with Walker 256 tumour using Talalay's method.[10] Ten days later, in 76 rats, bilateral takes were noted. From these, 52 animals were selected with tumours strictly comparable in size (rough diameter of the legs 3 to 3.5 cm.). On the same day these rats were weighed and separated into two groups and the experiment was started. In the first group (20 animals, mean body weight 194 gm. 5 c.c. of tumour-pouch liquid was injected at once into the jugular vein, the second group (12 rats, weighing 196 gm.) receiving 10 c.c. of the same liquid in a single intraperitoneal injection. The remaining 20 animals, mean body weight 202 gm., were used for the experiment with immobilization.

Results.—In both groups, a hæmorrhagic reaction in the tumours was visible through the skin 1½ hours after the injection of tumour-pouch liquid. Later, the legs bearing tumours became cold. Then, the majority of the animals

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became lethargic and some of them went into shock. As indicated in the table, the peak of mortality occurred between six and 16 hours following the injections. To secure tissues in good condition for histological study, some animals were killed while in a moribund state. They are indicated in the table as "dead." The mortality rate and mean body weight loss are summarized in Table I.

At autopsy, all tumours were hæmorrhagic, necrotic and liquefied. The main visible cause of death was a hæmorrhagic œdema of the lung. Animals injected intraperitoneally also had clear liquid in the pleural cavity. As the table shows, three animals of group I and two animals of group II survived more than 40 hours. All these animals were at this time in good general condition. At varying time intervals they were killed, autopsied and tumour tissue taken for histological study. At autopsy, the tumours of these animals showed the same degree of hæmorrhagic necrosis as the animals dying hours before.

TABLE I.

Group	*Number of animals*	*Initial body weight*	*Experimental procedure*	*Mortality*		*Mean loss of body weight after first 16 hours*	*Condition of tumour*
				hours	*dead*		
I	20	194	Tumour-pouch liquid intravenously	6 16 24 45 70	5 11 1 2 1	7 gm.	Extensive hæmorrhagic necrosis with liquefaction
II	12	196	Tumour-pouch liquid intraperitoneally	6 16 64	1 9 2	7 gm.	
III	20	202	Fatal stress	6 16 24 45 64	1 1 6 4 8	23 gm. (after 24 hours: 25 gm.) (after 64 hours: 46 gm.)	Damage limited to central necrosis

The histological changes in the Walker tumour, after the injection of tumour-pouch fluid, paralleled the macroscopic findings: there was vasodilatation with hæmorrhages and necrosis as well as degenerative changes in the tumour cells (pyknosis, pyknomitosis, chromatolysis and nuclear vacuolization) throughout the entire neoplastic mass (Fig. B, C). It is noteworthy that degenerative changes were constant throughout (including the periphery of the tumour) and even microscopic tumour nodules at a distance from the principal mass were destroyed. Incidentally, one animal of group I had a pulmonary metastasis (5 mm. in diameter) which also underwent hæmorrhagic-degenerative changes.

Since administration of large quantities of tumour-pouch liquid had toxic effects, we exposed another group of animals to severe stress, as a control for comparison with non-specific effect.

EFFECT OF FATAL STRESS ON THE WALKER TUMOUR

Material and methods: 20 Sprague-Dawley rats, prepared as indicated in the previous experiment, were submitted to the combined stress of immobilization and complete food and water deprivation. The immobilization procedure was the following: to the neck of the animal a wooden applicator was applied. Then the animal was strapped with its back tightly against a wooden applicator with adhesive tape, care being taken that respiration was not impaired. The incisors were then immediately clipped to prevent the rat from gnawing itself or the bandage. The animals thus immobilized (lying on their backs) were fixed to the table with another piece of adhesive tape. They were left in this position till death.

Results.—The mortality rate and loss of mean body weight are indicated in Table I. In no instance did we find the picture of massive hæmorrhagic necrosis which was observed after injection of tumour-pouch liquid. Two animals had an effusion of blood into the leg muscles and around the tumour mass, due to the mechanical compression of the immobilizing bandage. Microscopically, even these two animals did not show hæmorrhagic necrosis in the tumours. In all the animals under stress a hardening of the tumour mass was palpable.

At histological examination, degeneration and necrosis were observed in the central parts of large tumours only. Small tumour nodules and the periphery of the neoplasms showed no detectable changes. The histological picture of hæmorrhagic necrosis, as observed after admin-

istration of tumour-pouch liquid, was never observed after this stress-inducing procedure (Fig. D). In some animals under stress, independently of the length of survival, the tumour stroma was atrophic and mitoses were scarce. We would point out particularly that even animals which recovered from treatment with tumour-pouch liquid showed the characteristic extensive destruction of neoplasms which was not observed in rats dying from stress.

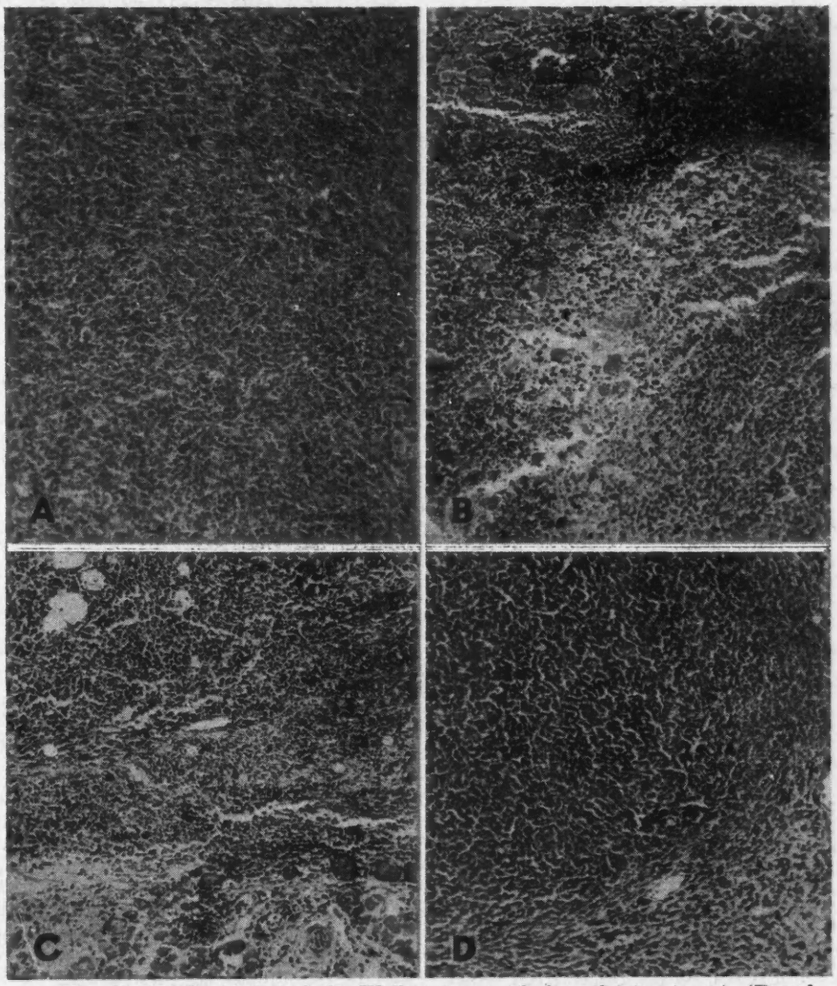

Fig. 1.—(A) Structure of the Walker tumour before the treatment. (B and C) After the administration of tumour-pouch liquid, the hæmorrhagic necrosis occupies the entire tumoral mass including the parts immediately adjacent to surrounding tissues. (D) The periphery of the tumour (extreme right), after a fatal stress, is of normal appearance; in the centre, degenerating and normal cancer cells are intermixed. The tumoral tissue is less dense than in non-treated animals (compare with A).

Therefore, a condition of stress in itself can induce regressive changes in the Walker tumour. Although after the injection of tumour-pouch liquid the morphological changes observed in this neoplasm are different, it is to be expected that here also the condition of stress plays a certain part. It is yet to be determined whether other factors, influencing the structure and biological behaviour of cancer, combined with severe or fatal stress, may induce destruction of malignant tumours, including metastases. Also, the co-existence of topical stress (such as inflammation in the tumour mass) and systemic stress might have a profound influence on neoplastic growths.

INFLUENCE OF SMALL DOSES OF TUMOUR-POUCH LIQUID ON THE GROWTH OF WALKER TUMOURS

We now wanted to determine the effects of the tumour-pouch liquid when administered in small, non-fatal doses. We adopted a procedure currently used by the U.S. National Cancer Institute for the screening of chemotherapeutic agents.

Material and methods.—In 24 female Sprague-Dawley rats the Walker tumour was implanted by the Talalay technique;[10] 24 hours later, the rats were weighed and divided into three groups. A first group of 8 rats (mean

body weight 186 gm., was injected intraperitoneally, with 5 c.c. of tumour-pouch liquid, on three consecutive days. Group II, also consisting of 8 rats (mean body weight 172 gm.), received 1 c.c. of tumour-pouch liquid into the jugular vein on three consecutive days. The controls in group III (mean body weight 182 gm.) were not treated. On the 7th day after the first injection the animals were again weighed, killed and carefully examined for the presence of tumours. The implantation sites (whether they contained visible tumours or not) were fixed in Susa, and stained with hæmatoxylin-eosin for microscopical examination.

Results.—All animals survived up to the end of the experiment. The mean final body weight in group I was 194 gm., in group II 183 gm., in group III 196 gm. Thus, there was no loss of body weight in any of the groups. At autopsy, two animals in group I, one in group II and eight controls had macroscopically detectable Walker tumours. In all rats injected intravenously or intraperitoneally with tumour-pouch liquid, the site of implantation or the developed tumours showed fine hæmorrhagic spots. Histological examination revealed the presence of minute tumour nodules in two animals of group I (intraperitoneal injection of tumour-pouch liquid) and in three of group II (intravenous injection of tumour-pouch liquid). Thus, in group I, four positive "takes" occurred (two macroscopically and two microscopically detectable). In intravenously injected animals (group II), one macroscopic and three microscopic Walker tumours were detected. The control, non-injected rats (group III) had macroscopically visible tumours in 100% of the cases.

In one series of similar experiments, we injected the tumour-bearing rats with a tumour-pouch liquid collected from 6-day-old pouches. Here, no effect on the tumour growth was observed. On the other hand, the liquid collected from 28-day-old tumour-pouches (with very extensive central necrosis) was more toxic and showed diminished antitumoral properties. Perhaps, the antitumoral activities of the liquid reach a peak at a definite time.

It appears that in the tumour-pouch liquid some biologically active substances accumulate, which can elicit hæmorrhagic, degenerative and necrotizing reactions in the same kind of tumour. Small, not particularly toxic doses of tumour-pouch liquid can lower the number of "takes" and limit the growth-rate of intramuscular Walker tumour implant. This is perhaps due to the combined effect of systemic stress, capillary toxins and—presumably—some biological antitumour substances, but the possibility of bacterial products originating from micro-organisms living symbiotically with the tumour tissue also remains.

DISCUSSION

In these experiments, we attempted to verify Ewing's hypothesis of the possible beneficial effect of tumoral exudates in neoplastic disease. This hypothesis necessarily assumes that under particular conditions biological control of cancer may occur. The results of our experiments render this view more probable. It must be kept in mind, however, that a phenomenon of cancer destruction, such as we observed, could be due to various mechanisms.

First we may mention substances originating in the tumour tissue itself (natural growth-inhibiting and growth-stimulating substances, steroids, or other substances not yet identified). Secondly, we must consider the host's response to the neoplasia, including local responses (e.g. inflammation and inflammatory substances; "defensive enzymes") and systemic responses (e.g. stress mechanisms, endocrine system, immunobiological process). Thirdly, such a response may be due to causes unrelated to the cancer (e.g. intercurrent infections and bacterial toxins).

It is clear that in our experiments one or several of the above mentioned mechanisms may be involved. Before attempting to analyse the mechanism of this tumour inhibition or to make generalizations from it, confirmation under varying experimental conditions and also by other laboratories is awaited.

SUMMARY

It has been shown that the liquid accumulating under certain conditions in the Walker 256 tumour exerts lytic properties against the same neoplasm. A technique is described which permits the collection of such tumour liquid in large amounts.

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Case Reports

LARGE BOWEL OBSTRUCTION WITH ACUTE APPENDICITIS

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THIS CASE is presented because the common condition of acute appendicitis was found concurrently with obstruction of the right colon.

CASE HISTORY

The patient, a man of 46, was awakened at 1 a.m. on May 26, 1952, by severe upper abdominal cramps. The pain appeared to last for about five minutes, and was severe enough to cause him to move around in bed and to sweat slightly. It would then subside and be absent for about 15 minutes when it would recur. There was no steady pain, no accompanying nausea, no vomiting, no diarrhœa, no desire to defæcate, no urinary disturbance and no previous history of indigestion, abdominal pain or food intolerance. The pain continued in the same manner for five hours when it became less severe. Examination revealed normal pulse, temperature and respirations. There were no clinical findings in any other system except the abdomen, which was soft, not tender, and not distended, with no evidence of peritoneal irritation. At the time of a severe cramp, there was some voluntary splinting of the abdomen but no particular tenderness. The pain subsided approximately 15 hours after its onset.

Urinalysis was negative. The leucocyte count was 13,500, with 84% polymorphs; erythrocyte sedimentation rate 16 mm.; icteric index 9.5. A plain film of the abdomen revealed no radio-opaque gall stones or urinary calculi.

On May 27, he spent a comfortable day with occasional intermittent cramp, which was not as severe as those originally present. This state existed throughout this and the following day, no tenderness being elicited in the abdomen during this time. Urinalysis remained negative throughout. The white cell count was 12,800 with 78% polymorphs on May 27 and 8,400 on May 28. Temperature and pulse rate did not alter. He slept well the night of May 28, but was awakened at 7.30 on the morning of May 29 with a severe attack of steady generalized abdominal pain. This was accompanied by an increase in pulse rate to 96, and respiration rate to 22 and no change in temperature. Examination of the abdomen revealed no distension; there was generalized rigidity and no point of maximum tenderness. Rectal examination revealed no significant finding.

The abdomen was opened through a right paramedian incision extending equally above and below the umbilicus. The peritoneal cavity contained a considerable amount of small bowel content. A gangrenous perforated pre-ileal appendix was surrounded by indurated great omentum and lay against the supero-lateral aspect of the small bowel mesentery. From the small bowel mesentery running laterally across the ascending colon to the right colic gutter lay a thick, dense, firm adhesion, measuring 0.5 by 0.5 cm. and markedly constricting the ascending colon by making it pass through a tunnel the size of a lead pencil. The cæcum was somewhat larger than usual but was not tense or distended because spontaneous defunction had been carried out by perforation of the gangrenous appendix. The adhesion was cut, appendectomy was performed, and the pelvis was drained by latex drains through stab wounds in the iliac fossæ.

Postoperative care consisted of Wangensteen suction drainage for 72 hours, maintenance of fluid and electrolyte balance, semi-Fowler position, chemotherapy and ambulation on the sixth day. The postoperative course was excellent and without fever and the patient was discharged from hospital with the drainage wounds dry on June 14. A year and a half later, he remained in good health.

We do not know which lesion was primarily responsible for this episode. Because of the firmness and thickness of the obstructing adhesion and the resulting remarkably small tunnel through which the right colon passed, we are inclined to think that this lesion had been present for some time without symptoms. It is conceivable that the obstruction in the colon was the primary lesion, creating sufficient back pressure to initiate obstructive appendicitis. The acute gangrenous appendix lying in the same region as the origin of the band from the supero-lateral aspect of the small bowel mesentery, by the very nature of the accompanying inflammation and induration of the area, may have tightened the band further, thus increasing the pressure in the cæcum and appendix, so setting up a vicious circle until perforation took place.

The need for dealing with both these lesions at the same time is evident, and the corollary is obviously that the exposure needed to be adequate for recognition of both lesions. Had the diagnosis of acute appendicitis been made at an earlier time, it is possible that the obstructing band might have been overlooked at operation through a McBurney incision.

CONCLUSIONS

1. This case demonstrates what is well known, that there is nothing typical about some cases of appendicitis.

2. A case of obstruction of the ascending colon by an adhesion with spontaneous intraperitoneal defunction through a ruptured gangrenous appendix is presented.

3. Exposure through a McBurney incision in this case might have been inadequate to reveal the two concurring lesions.

4. Had the case been diagnosed as acute appendicitis at an earlier stage, a McBurney incision might well have been used and the obstructing lesion in the colon might have been missed, with disastrous results.

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ACUTE INTERSTITIAL PANCREATITIS IN A TEN YEAR OLD GIRL

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PANCREATITIS is uncommon in children. The types which have been described are: chronic, chronic relapsing, traumatic, secondary, acute, and hæmorrhagic. Occurring in the course of or after an acute infection, secondary pancreatitis is fairly well recognized, especially if the infection is mumps; scarlet fever, typhoid fever, diphtheria, malaria, pneumonia and influenza have been reported to carry pancreatitis in their wake.[7] Traumatic pancreatitis is, of course, secondary to injury. The acute hæmorrhagic form is severe and usually fatal, while chronic pancreatitis has been variously described as a progressive condition and as a series of acute attacks.[1, 2]

Acute interstitial pancreatitis unassociated with a systemic infection and occurring in a mild form in a child does not appear to have been described, and this case is therefore presented.

G.B., a ten year old girl of high intelligence, was seen on October 27, 1953 complaining of dull nagging abdominal pain, which had been present on waking three days previously and had persisted without much change until the time of examination, and anorexia. When asked for the site of the pain she circled the umbilicus with her fingertips. The pain was constant, did not radiate, and was not felt at any other site. She had a marked distaste for food (without special reference to fats), and had taken practically nothing but fluids, and these only in small amount since "even a small drink of warm water" made the pain worse. She had not vomited nor had any urinary symptoms. On the second day of the illness she was given a laxative because her bowels had not moved: a small stool was produced but its colour was not noted. She had not reached the menarche.

Her temperature was 100.4° F. and pulse 104. The tongue was dry and the breath fœtid. Positive physical findings were limited to the abdomen, which was normal in contour; there was no guarding except inconstantly in the right upper quadrant and epigastrium. Pressure over any part of the abdomen caused pain in the umbilical region, as did the tip of the finger inserted into the rectum, and rebound tenderness was present throughout. Central pain was felt on stretching the psoas muscle. There was doubtful hyperæsthesia over the right side. The urine was concentrated but otherwise normal. There was a moderate leucocytosis (15,100 per c.mm.). Abdominal radiography showed no abnormality except an accumulation of gas in the stomach and large bowel. A provisional diagnosis of mild acute appendicitis and/or mesenteric lymphadenitis was made.

After the patient had been anæsthetized (thiopentone, decamethonium, and oxygen), a hard mass about the size of a golf ball could be felt in the epigastrium just to the right of the midline. A right paramedian incision was therefore made from the costal margin to the umbilicus. The mass proved to be the head of the pancreas: the whole organ was swollen and nodular, and greyish in colour. Numerous enlarged mesenteric lymph nodes were found and an apparently normal appendix was removed. The gall-bladder was normal and contained no stones. There was no Meckel's diverticulum. The pathological report on the appendix was "periappendicitis—acute—mild".

Dicrysticin had been given preoperatively and was continued for five days. She was given a high-carbohydrate, low-fat diet and made a rapid recovery, although her appetite returned more slowly. Three months later she was completely well.

Serum amylase and lipase values one month after the operation were normal, and no evidence of helminth infestation was found in the stool.

DISCUSSION

While other writers[2, 7] emphasize that a mild secondary pancreatitis may pass unrecognized, it is nowhere suggested that an obvious pancreatitis may follow an unrecognized infection. In this case the mesenteric lymphadenopathy may have been the primary source of infection, or the "periappendicitis". The fact remains that this girl presented with symptoms of abdominal pain and anorexia and no history of preceding illness.

In 1935 Dobbs[3] summarized all the cases of pancreatitis in children he could find in the literature. These numbered 14 and only two were mild. One of these was associated with gallstones for which operation was performed, a pancreatitis being discovered incidentally. The second was associated with roundworm infestation, as were two of the other (severe) cases.

Although no amylase estimations were performed at the time in this case, the history and findings in retrospect strongly suggest that the symptoms were due to pancreatitis. The progress of the case shows that it was a benign and short illness, and it is certainly unlikely that the penicillin and streptomycin given aborted a potential acute hæmorrhagic pancreatitis. A diagnosis of acute mild pancreatitis is therefore justified. Attention is drawn to the simulation of acute appendicitis.

These conclusions may be premature and time may show this to be a chronic or chronic relapsing pancreatitis, but when complete recovery follows a short illness, as in this case, the latter must be considered as an entity until proved by the subsequent course of events to be otherwise.

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VAGINAL ATRESIA

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VAGINAL ATRESIA is an entity to which little textbook space and less lecture time is devoted. Yet its occurrence may cause confusion unless the physician is at least aware of the possibility of its existence in any age group. The extent of this anatomical defect varies from mild narrowing to complete absence of the vagina.

The causation of this uncommon condition is somewhat obscure. About the congenital variety there is not complete agreement, and indeed various lesions may arise from different maldevelopments. Embryonic arrests at or about the 50 mm. length, branching or reduplication of the original vaginal plate, longitudinal and lateral extensions of the mesonephric (Wolffian) duct as it progresses into the duct of Gaertner—are three good springboards for conjecture. As yet this knowledge is of more theoretical than practical value to the surgeon. Atresia of the acquired variety may result from traumatic factors, neoplasms or inflammatory lesions. Hormonal influences also exist.

There are several different methods of treatment. Where consistent co-operation of the patient can be expected, the Frank non-surgical method of making an artificial vagina is gaining in popularity. This is the glass rod method mentioned later. Various surgical procedures are employed. The Wharton operation (1932) for construction of a vagina is not difficult, nor is the method of Falls (1940). The latter gives satisfactory results with no complaint of undue dryness of the epithelium. There is also the Graves operation for congenital absence of the vagina, and its modifications (Leo Brady, etc.).

The following is a brief report on such a case.

In March 1953, a 40 year old nullipara presented herself in my office. Five months before this visit she had noticed slight vaginal spotting midway between her menses. It had never happened before or since, and she did not at the time notify a physician. During the past week she had experienced some dyspareunia, and mild bleeding after intercourse. It was for these complaints that I was being consulted. This woman was a trained nurse from a leading American hospital and knew of the possible causes and consequences of abnormal bleeding per vaginam.

Her personal history was not of great significance. Two years before she had married and marital relations had been normal. She had never been pregnant. She had a 28 day menstrual cycle with moderate flow, commonly no pain, infrequently slight discomfort. Her last menstrual period had ended 19 days previously and had been perfectly normal. She was unable to recall any incidents suggestive of a tendency to bleeding. The family history was non-contributory.

The general physical examination showed nothing remarkable apart from the pelvic examination with the patient in lithotomy position.

The vaginal orifice admitted two fingers but about 2½ inches within the canal the walls narrowed sharply like a funnel. The cervix was only indistinctly felt. A bivalve speculum was inserted with a good light; when the blades were gently opened, the external os of the cervix was just revealed; the bills of the instrument could not be pushed beyond the cervix tip anteriorly or posteriorly; neither fornix appeared present. There was about a 1 cm. circle of inflamed vaginal mucosa, seemingly adherent to the entire circumference of the external surface of the cervix near the os. This was acutely reddened and could well have been the site of origin of the blood alarming the patient.

Within the next few days she was admitted to hospital and examined under anæsthesia. A further gynæcological consultation at that time confirmed the diagnosis: atresia of the upper two thirds of the vagina.

The bleeding was probably traumatic, from the penis striking the inflamed area at the junction of vaginal and cervical mucosa; this could also account for the pain during intercourse.

Mr. J. Lyle Cameron, F.R.C.S., of London, Eng., writes me:

"The incidence of stenosis of the upper two-thirds of the vagina is very rare. You are wise in reporting this case; several of such should be recorded for the help of future surgeons. I have seen two complete absences of vagina, both of which were operated on by Sir Archibald McIndoe. Numerous operations which utilize small bowel loops and colonic loops have been described—by Bonny (small bowel), and the second by Sir Ernest Rock Carling. McIndoe's work, however, I consider to be the only satisfactory one.

"He makes a space between the bladder and urethra in front and the rectum behind. A Thiersch graft is cut from the inner side of the thigh and placed around a stent mould of considerable size to which the graft is firmly attached by painting with Mastosol. When the space is opened up the stent mould, covered with the graft, is inserted into the space, whether this be the whole or part of the vagina (it matters not), to be covered by epithelium. The vaginal entrance is then sewn together in such a way that the mould remains in place for six months at least. By this time cicatricial contraction will have occurred to its fullest extent, and there will be no further contraction.

As regards a case such as this, I would advise that you open the vagina forcibly with specula, probably the long and narrow bladed specula described by Maingot. Several longitudinal incisions, probably laterally, should be made so that the vagina can be sufficiently stretched to take the large stent mould, which is about four and a half inches long and about two and a quarter inches in diameter. Cover this mould with a flap of skin shaved off the inner side of the thigh; the flap being held to the mould with Mastosol. Insert into the newly opened up space and suture so that it may not come out for a year. The stent mould is hollow so that menstrual fluid and cervical mucus can easily escape."

Dr. H. B. Atlee, Chief of Gynæcology, the Victoria General Hospital, Halifax, N.S., contributes:

"We recently had a case of atresia of the upper third of the vagina. She was a young woman who had had hæmatocolpos but the closure was not the usual familiar one of canalization of the immediate lower end of the

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Mullerian ducts. There was an actual atresia of the vagina. The doctor had opened up the vagina because of the hæmatocolpos, which of course was an urgent factor in her case at that time. When we saw her a month ago she wanted to get married and all we could find was a small fistulous tract into which, with considerable difficulty, a probe could be inserted and led to the upper vagina in the region of the cervix.

"The part of the vagina stenosed appeared to extend from the junction of the middle and lower thirds upwards to within about ¾" of the cervix. We broke this down with sharp and blunt dissection and found a normal cervix but were left with no mucosa whatsoever in about one-half of the vagina. We therefore made a cylindrical hollow mould of acrylic and left it in her vagina. We have sent her home and expect that after two to three months of wearing this mould constantly her vagina will completely epithelialize.

The other case I saw recently was in a girl who had no vagina except a tiny dimple. In her case I was using the method with a glass rod almost ½" in diameter. The girl pushed this every day into the little pit and gradually elongated it, and when after a month or six weeks she got it up to 3-4" a larger stem was used until the largest size vaginal dilator could be inserted. After about a month she has a passageway about 3" long and I am getting her a larger rod."

Dr. R. W. TeLinde from Johns Hopkins Hospital writes:

"I can recall seeing only two cases of atresia in the upper vagina. One was congenital. There is a picture of it and a description of the operation in the second edition of my *Operative Gynæcology*. The operation simply was the resection of a septum at approximately the junction of the upper and middle thirds of the vagina and then anastomosing the upper and middle thirds. This was a very simple procedure. She has menstruated normally since.

"The other case I had occurred in a virgin of 40. The upper portion of the vagina simply contracted and obliterated itself. I do not believe that this was a congenital affair, but rather had some kind of inflammatory basis. She had no symptoms until about six months before when she developed very severe dysmenorrhœa. The pelvic findings were suggestive of endometriosis. I performed hysterectomy and found endometriosis on the posterior surface of the uterus. In these cases there is no point in attempting to restore the vagina to normal.

"If your patient is a younger married woman and it is necessary to preserve the vagina, I presume the only thing you can do is to dissect out the space in the upper vagina and perhaps keep it open with a vaginal form until it becomes completely epithelialized."

In summary, atresia of the vagina, while rare, does occur in various degrees, presents itself in different ways, can cause embarrassment, and is amenable to treatment.

I should like to express my gratitude to those who have so kindly written me about this case.

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EROSION OF BONE PRODUCED BY GLOMUS TUMOUR*

W. ROBERT HARRIS, M.D., *Toronto*

TUMOURS of the myoneural apparatus controlling the arteriovenous shunts of the peripheral circulation are not uncommon. They have been adequately described under the heading of glomus tumours. Although involvement of bone by such tumours has been reported[1, 3] it is rare. The following is an account of a subungual glomus which had produced erosion of the underlying bone.

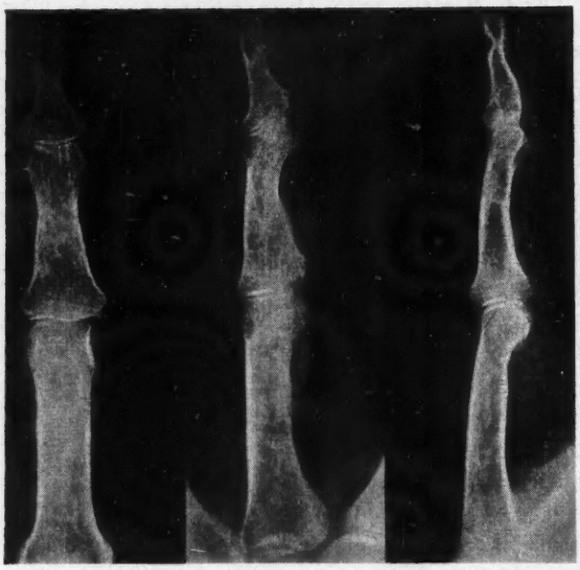

Fig. 1

A 59 year old jeweller had been incapacitated for three years by pain in his left middle finger. The pain was burning in character, and agonizing in degree. The only relief he could obtain came from holding his hand under running cold water. On examination the whole hand was warm and moist. The involved finger was held outstretched and protected by the other hand, and the patient was unwilling to move it. It had a dusky hue in contrast to its neighbours. The slightest pressure on the finger nail produced exquisite pain, and the blanching produced by pressure revealed a small spot of persistent purple colour. Radiographs of the finger revealed that at a point corresponding to the purple spot the underlying bone had been excavated (Fig. 1). The excavation was lined with cortical bone.

*From the Department of Orthopædic Surgery, Toronto General Hospital.

The lesion was excised after removal of the fingernail, exposing the bone of the terminal phalanx. Apart from being indented by the tumour the bone was not grossly involved. Removal of the tumour has brought about complete relief of the symptoms.

Bone lesions similar to those seen in this case have been produced by sebaceous or dermoid cysts of the fingers.[2] Only two cases of glomus tumour arising primarily in bone have been reported;[3] in these the x-ray change suggested an enchondroma rather than a cyst. In any case the pain of a glomus tumour is its characteristic feature, and therefore there should be little difficulty in diagnosis.

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Clinical and Laboratory Notes

INTENSIFIED MULTIPLE SHOCK ELECTROCONVULSIVE THERAPY*

EDWARD L. MARGETTS, M.D., *Montreal*

IN 1948, Page and Russell[3] reported the use of increased voltage and duration in the administration of electric shock treatments. They called their technique "intensified electrical convulsion therapy." Briefly, their method was to use 150 volts for one second, and to give up to nine more applications of this voltage *during the primary convulsion.* They have developed a special ECT instrument, "Ectron," made by Reeves Electrical and Radio Co. Ltd., Reelek Works, Baldock, Herts., England. This apparatus is a small (7½ x 4 x 4 inches) compact unit which is very simple in design and easy to use. It may also be employed for the conventional method of ECT.†

At the Allan Memorial Institute, we had been using the Coramine-electroshock of Fabing,[1, 2] which was sometimes found useful in agitated and excited patients and in those who did not respond to ordinary ECT. We determined to try a variant of the technique of Page and Russell, which we regarded as a "reinforced ECT," as we called the combined Coramine-electroshock and other intensified treatments, such as multiple shocks at one treatment period, or several treatments spaced throughout the day. A technique modified for use with Offner type 733 electroshock apparatus was devised. The method is as follows: the dials are set at 400 milliamperes and 1 second, and the lights are balanced. The current is then passed through the brain, and as soon as the mechanism clicks off, the procedure is immediately repeated four or five times by flicking the test switch, then the treatment switch, without resetting the lights and as rapidly as possible. In this way, the current passes five or six times *during one prolonged convulsion.* Intravenous barbiturate premedication is used in order to minimize apprehensive anxiety in the patient and blot out preshock memory. Muscle relaxants like curare or the newer paralyzants such as succinylcholine may also be injected. Treatments are generally given with the same spacing as ordinary ECT. Different settings of time and current than those mentioned above may be used, and indeed for some patients this is advisable. No unusual difficulty has been encountered with onset of respiration after treatment. Memory changes and confusion seem no more pronounced than with the ordinary method, provided that proper judgment is utilized in assessing the patients' responses, and that skill is indicated in applying the technique.

Dr. Franklin Offner, in a personal communication, writes as follows:

> ". . . Apparently control of the current after the initial convulsion can have important therapeutic results. . . . The Types 732 and 733 Electric Shock Therapy Apparatuses preset the treatment current according to the patient's electrical impedance. If this were to change more than approximately 15% during the multiple shock technique, the interlock would prevent giving additional shocks without rebalancing the lights (*i.e.*, resetting the treatment current to its desired value). The success of the technique described shows any impedance variation which may occur in general not to be of significant value. However, the possibility of a larger variation should be kept in mind, with the accompanying need of rebalancing the test circuit between shocks. . . ."

The procedure has been found a useful variation, and it is suggested that the method be tried by other clinicians on patients who have failed to respond to ordinary ECT. Most apparatuses can be adapted to the intensified multiple shock technique.

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*From the Allan Memorial Institute of Psychiatry and Department of Psychiatry, McGill University, Montreal, P.Q.

†Our experience with the "Ectron" apparatus leads us to believe that spinal compression fractures may be a more frequent complication than with other machines having controllable duration, type, and amount of electrical current.

The apparatus and technique as described in this paper has been used for five years with very few complications. We prefer it to the high voltage method, which we have discontinued.

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(Information regarding contributions and advertising will be found on the second page following the reading material.)

Editorials

THE COTTAGE HOSPITALS OF NEWFOUNDLAND

The cottage hospital system of Newfoundland was born of necessity. In an island with 1,500 communities scattered along a 7,000 mile coast, Newfoundland's medical services found transportation one of their major difficulties: there are very few roads, and transportation is mainly by water, although this too is obviously affected by weather conditions. The object of the cottage hospital system was to make hospital and emergency surgical treatment available to outlying areas; as a recent report comments, the grim necessity for surgery and emergency medicine took priority over preventive medical measures.

Each hospital is equipped with an operating theatre and x-ray appliances, and is directed by a doctor who has had surgical experience. The hospital can be regarded as the local "health centre"; at it, out-patient diagnosis and treatment and in-patient emergency treatment, including care of abnormal pregnancies, can be obtained for an annual sum of $10.00 for each family. This premium also covers the family for admission to the "base hospital" at St. John's, but does not cover the cost of medicines which are charged to the individual concerned. From the hospital domiciliary visits may be made by the doctor on the recommendation of the district nurse, who is closely connected with the local cottage hospital. Immunization, health education and free distribution of orange juice for pregnant women and infants under one are also organized from the local hospital. The doctor receives a basic salary with the addition of a proportion of all fees, and he is also paid for certain additional services.

Some other features of the Newfoundland medical services are of interest. For example; the provision of nursing services, mobile x-ray and tuberculosis teams, and pre- and post-natal treatment in outlying areas. The use of cabin cruisers equipped for medical care is also an innovation. Prevention of illness should, of course, be a primary function of any medical service: the government is acutely aware of this, as evidenced by its provision of free cod liver oil in the schools and its methods of health education.

PLAGUE

To the American city dweller, sheltered behind an efficient public health service, the subject of plague may appear of only slight interest. It may therefore seem a little unnecessary to draw the attention of the Canadian profession to the fact that one of the world's authorities on plague, Dr. R. Pollitzer, has just completed a monograph* of superb quality on the disease which has been his life's work. There are, however, a number of reasons why this fascinating disease, which has on two occasions—in Roman times and in the Middle Ages—rushed across the stage of history with devastating effect, should not be ignored by anyone concerned with health.

In the first place, the causative organism, *Pasteurella pestis*, is apparently actually present in Canada. Ground squirrels were found to be infected with plague in 1939-42, in 1945 and again in 1947, in the province of Alberta and later in Saskatchewan. It is clear that the epizootic has spread from the United States, where the disease first appeared in 1900 in California, having apparently being conveyed there by ship from Asia. "Thus far," says Pollitzer, "the existence of human plague has not been proven in Canada, but it is possible that one fatal case occurred in Alberta before the existence of wild-rodent infection had been established."

Secondly, it must be remembered that the present pandemic, which apparently started in China about 1855, spread very slowly until 1894 and then burst forth throughout Asia, has by no means burnt itself out. In 1952 there were 7,539 cases reported in India, 5,190 in Indonesia, over 1,000 in Burma and a little under 1,000 in Africa,

*Pollitzer, R., Plague. 698 pp. Illust. $10.00. World Health Organization. Geneva, 1954.

64 in Brazil, 39 in Ecuador and 25 in Peru. To quote Pollitzer again;

> "It would be wrong to assume that the infection has altogether lost its sting."
> "The spectacular decrease in the incidence of human plague is not by any means accompanied by a corresponding restriction of the areas in which the infection is present among the rodents. On the contrary, it must be realized that the extent of the areas in which the rodents are affected has become progressively enlarged during the present pandemic. . . . This is a situation which cannot be viewed with equanimity. . . ."

Thirdly, there is a great fascination about the study of plague for its own sake. The havoc which it can cause has captured the imagination of novelists like Albert Camus who in *La Peste* draws a vivid picture of the results which might accrue from the visitation of a modern seaport by the pestilence. The peculiar features of its spread and periodicity have attracted the attention of noted epidemiologists like Major Greenwood, and the anxious search for a means of mass prophylaxis has led to great activity on the part of the serologists.

A distinction is now drawn between rat plague and wild-rodent plague, the former being responsible for the simultaneous involvement of many individuals in an urban community, the latter for sporadic rural cases. The latter are the greater nuisance in North America. Urban epidemics can now be readily controlled, but there is a great danger of misdiagnosis of even well-marked plague cases in areas where medical workers are unfamiliar with the disease. Thus Link* in 1950 appealed to the physicians of the western states of the U.S.A. "to regard all cases of inguinal and axillary adenopathy with a high index of suspicion and institute immediate treatment with streptomycin and sulfadiazine." Fortunately, the danger of spread of plague from wild rodents such as ground squirrels and prairie dogs to "domestic" or commensal rats is slight, though it may have caused the 1924 Los Angeles epidemic. Commensal rats are to be found in Manitoba and Saskatchewan, where they appeared about 1900, but not in Alberta—another safety factor.

The question arises whether plague-bearing fleas could be carried into North America from endemic areas. This type of spread may, for example, have caused the endemicity in India since 1894, for there is a theory that the vector flea *Xenopsylla Cheopis* was imported in cotton bales from Egypt. However, tests made in the U.S.A. suggest that this is a remote danger. Few fleas survive the carriage for long distances by sea.

Pollitzer records the radical change in outlook which modern therapeutic methods have brought, both in bubonic and in pneumonic plague. He incidentally mentions the proposal to call the former zootic plague, since it is conveyed from rat to man, and the latter demic plague, since it is conveyed from one human case to another. Streptomycin, which was the first drug to cure pneumonic plague, has relegated sulfadiazine to second place in treatment, and in Pollitzer's opinion made the production of therapeutic serum a waste of money. Serum is equally valueless in prophylaxis, though the use of a vaccine is approved.

The other prophylactic measures are the use of insecticides, such as DDT, and rat control measures. Pollitzer considers that the advent of DDT has not obviated the need for rat control, though it is a depressing thought that rat-destruction campaigns may serve only to produce a compensatory increase in fertility of survivors. Rat-proofing is by far preferable to killing campaigns, but it is often necessary to combine the former with measures for wild-rodent control.

In conclusion, the lesson for us to draw from this model among monographs seems to be, "Do not let us worry about plague, but do not let us forget about it either." It remains to express the wish that this standard work on plague may bring to the author the general recognition due to a modest, courageous and outstanding scientist.

*Link, V. B.: *J. A. M. A.*, 144: 375, 1950.

Editorial Comments

VISUAL ACUITY AND NIGHT-DRIVING

The continuing toll of road accidents is one of the penalties of modern civilization, but education of the driver and the manufacturer can help in reducing this toll. When driving at night the driver studies the road at the distance limits of his headlights, and any decrease of illumination will obviously delay his reaction time. The driver's eyes become adapted to the average reflection of the lights of the head lamps from objects both on and off the road. for example, the reflected light off a white dividing line is 70%, while off a black top is only 10%. Paul Miles,* in commenting on night-driving, points out that a combination of pink glasses and green wind-

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shields produces a very serious reduction in visual acuity. Green-tinted windshields are useful for daytime-driving because they cut out red and infrared rays which carry heat; on the other hand, almost two-thirds of a headlight's power is concentrated into the red end of the spectrum and obviously two-thirds of the headlight's power is removed by using a green windshield.

Experiments under night-driving conditions and using Snellen's charts are of great interest. Visual acuity was reduced from 20/32 to 20/40 with pink glasses, to 20/46 with a green-tinted windshield and to 20/60 with a combination. Miles also comments that two objects would appear separate at 100 feet in the path of headlamps, but, using a green windshield, they would appear single, till a distance of 25 feet. Similarly stereoscopic acuity, discrimination of velocity and direction of a live target, are also defective using a green-tinted windshield at night. It is suggested by the author that green-tinted windshields should be detachable so that they can be removed at night.

The implications of this work are interesting. Should manufacturers of automobiles take these experiments into consideration as regards green-tinted windshields? Or should the public be warned of the dangers and left to draw their own conclusions? W.F.T.T.

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THE ABRAMS MACHINES

Those who follow the various forms of undesirable exploitation in the field of diagnosis will be interested in the recently announced action of the U.S. Food and Drug Administration regarding a number of so-called electrical devices for diagnosis and treatment of disease. The Department has entered an injunction decree barring from interstate commerce 13 such devices, of which there are about 5,000 in the offices of various "fringe" practitioners. The names of the machines run the entire scale of bombast and imposture: from such trifles as "Oscilloclast," "New Depolaray Junior" to the "Sinusoidal Four-in-One Shortwave Oscillotron." At least there is no slavish copying of names.

In its injunction the Government charged that all the devices named are misbranded, since "they are not capable of diagnosing or curing any disease." They are distributed by the Electronic Medical Foundation of San Francisco whose activities apparently consist of a "blood diagnostic" service and the selling of these electrical devices. The diagnostic service does not burden its clients with exacting requirements. By simply sending in a drop of the patient's blood on sterile(!) paper the seeker after truth would, for a fee, receive a full diagnosis of the patient's trouble. Apparently it made little difference whether the blood was human or animal, or even blood at all. In test cases blood from roosters, hamsters and from a dead man all drew forth detailed diagnoses including tuberculosis, melancholia, and "mixed toxins of the colon." A spot of coal-tar dye sent as the blood of a woman accounted for a diagnosis, at least etymologically correct, of anæmia! The blood of an amputee was reported as representing arthritis, which must have been of the phantom variety as it was diagnosed as being in the right foot which the man had lost several years before.

The diagnostic machines themselves are no less weird. The radioscope of the Foundation was a "tuning apparatus" which it was claimed could distinguish diseases by their radio frequencies. It consisted of a box with dials, lights and wires, and it will come as no surprise to add that these lights are of a variety of colours. An "electronic reaction" is obtained by stroking with a wand the abdomen of a person who is called the "reagent." If the wand (plastic of course) sticks to any one part this gives the clue to the diagnosis in full.

As might be expected, this Foundation was set up by the late Dr. Albert Abrams, who invented the machines to perpetuate his electromedical theories and incidentally to coin a great deal of money. The present director of the Foundation is not discouraged by these legal restrictions. He is going to continue his "research" on the utility of the devices in Germany and Mexico. He has fully absorbed Dr. Abram's real discovery,* which was that there will always be numbers of people who will believe anything they cannot understand, and more important still will pay for being duped. In other words, "There's one born every minute!"

LITIGATION IN MEDICAL PRACTICE

There has been in Great Britain a decided increase in litigation involving patients and hospitals and their medical staffs since the introduction of the National Health Service. There must be many reasons for this. A recent letter in *The Lancet* from a lay correspondent suggests that in her experience one definite factor is the unreasonable unwillingness, or at least failure of doctors in hospitals to give parents and relatives information on the patient's condition. There is much to be said on both sides, but at the moment we shall refer only to an aspect of the manner in which it is being dealt with, as discussed in *The Lancet* (1: 713, 1954) under the heading, "Who is to pay for mistakes?"

At first under a ruling of the Ministry of Health a hospital authority which had been assessed damages was expected to reduce its own pecuniary loss by taking suit for part of this against any member of its staff whom it considered to have been negligent in the case. The detrimental effect of such an arrangement was all too obvious: it was possible on occasion for

*See "The Medical Follies": Morris Fishbein: Boni & Liveright, New York, 1925.

a hospital authority, in defending itself against a charge of negligence, to provide evidence against its own medical staff.

This situation has now been corrected to this extent (under representations from the British Medical Association) that where the doctor concerned is a member of a defence society, and that body accepts responsibility for him, any payment to the plaintiff is to be apportioned between the doctor and the hospital authority, as agreed between them, or if no agreement can be reached, it will be shared equally.

In addition, it is realized by the defence societies that there may be cases in which, although the hospital alone is cited, the doctor concerned might quite properly be asked to make a contribution towards the amount paid to the plaintiff by the hospital, on the ground that the practitioner's action was a material factor in the negligence complained of. And the converse might arise as regards the hospital, where the doctor alone was cited. The Ministry's decision left this to the co-operation of both parties.

The Lancet comments on this as a welcome change, but is not quite sure but that it may contain undesirable implications. Where either the hospital or the doctor alone settles a case, or where by arrangement both share (even if one only is cited), there can be no objection. But if in time there should develop a feeling that hospitals should share in damages against doctors there might be justification in the introduction of more and more small rules for doctors. And that would lead to undesirable lay regulation of clinical work. *The Lancet* would have the doctor lose none of his professional freedom by giving up any of his professional responsibility.

DR. H. G. GRANT

It is with extreme regret that we learn of the death on May 8, of Dr. H. G. Grant, age 64, Dean of Dalhousie Medical School. Fuller notice will appear in our next issue.

Men and Books

THE WRITINGS OF MICHAEL SERVETUS

S. S. B. GILDER, M.B., *Montreal*

IT IS COMMON KNOWLEDGE that Michael Servetus, whose claim to medical fame is based on his description of the pulmonary circulation, was burned at the stake as a heretic just over four hundred years ago. The 400th anniversary of this event, which was observed on October 27, 1953, was noticed in the medical press of many countries last year, and both the burning at Champel, a suburb of Geneva, and the quarrel with Calvin which led to it are well documented. The earlier details of the life of this highly intelligent and versatile but singularly foolhardy martyr are by no means so well known, and his contributions to geography, astrology, theology and medicine have so far been accessible only to scholars with a knowledge of Latin.

The appearance of a well-annotated translation of certain works by Servetus, for the most part rendered into English for the first time, will therefore be welcomed by medical historians. The translations have been made by Professor Charles D. O'Malley* of Stanford University, with some assistance from the Department of the History of Medicine in Yale University, and the author has tried to produce a literal rather than an elegant version, in order to avoid twentieth century interpretation of sixteenth century statements.

A study of these translations confirms the view that Servetus was a difficult man in his personal relations. If ever a man may be said to have brought a violent death on himself, it was this obstinate Spaniard. The way in which he baited and insulted Calvin without any particular provocation, and then showed himself publicly in Geneva, a city in which Calvin was more powerful than any king, is a matter of common knowledge, but this was only one episode in a life of bitter controversy. Furthermore, on the occasions when the fury engendered by his behaviour impelled him to publish some explanation, the latter seems to have had the effect of making matters worse. His troubles started at the age of nineteen when he took upon himself to correct the theology of the leaders of the reform movement in Basel in a tract *De trinitatis erroribus;* his later attempts at explanation in *Dialogorum de trinitate* did nothing to calm the storm that had broken about his head, so that finally he was compelled to depart and begin a 21-year life under the pseudonym of Michael Villanovanus.

In Professor O'Malley's work, there are two translations illustrating the same trait. The first is an *Apology against Fuchs,* a German physician and botanist, with whom Servetus indulged in a pointless and acrimonious dispute about the newly revived Greek medicine. In his Apology, Servetus speaks of the "impudent boasting" and the "poisonous fangs" of Fuchs, to whom he also applies the adjectives "harsh", "insolent" and "savage". Fuchs does not appear to have replied to this attack, which apparently represents Servetus's first excursion into the field of medicine in 1536.

The *Discourse in Favour of Astrology* (1538) also translated by O'Malley, is no better calculated to spread sweetness and light. Servetus was at this time giving lectures on mathematics and

*Michael Servetus. C. D. O'Malley. 208 pp., illust. $3.00. American Philosophical Soc., Philadelphia 6, Pa., 1953.

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astronomy in the University of Paris, and had gradually strayed into judicial astrology or the forecasting of events by observation of the stars. This practice was at the time regarded as unethical behaviour, and Servetus was ordered to discontinue his lectures. As usual, Servetus made no attempt to obey the injunction, but proceeded to prove the medical faculty wrong in an essay based almost entirely on the literal interpretation of such authors as Hippocrates and Galen. This piece of impertinence led to his disappearance from Paris.

From the medical standpoint, the most important work translated by O'Malley is a treatise on the *Syrups*, published in Paris in 1537 and founded on no medical experience whatever but on a close study of Aristotle, Hippocrates and Galen. His purpose in publishing the treatise was apparently to support the new Greek school of medicine against the Arabists. Much of the translation would be unintelligible to anyone unacquainted with Galenical medicine, but Professor O'Malley gives sufficient explanation to enable the reader to follow fairly well the closely-reasoned arguments in the text. The syrups which he describes had of course a much wider range of action than those of modern times, being used for example as diuretics, purgatives and emmenagogues.

The six pages of medical interest from the work which sealed Servetus's fate [*Christianismi restitutio* (1553)] are reproduced in translation. It is clear from the text and Professor O'Malley's explanations that the description of the pulmonary circulation given in these pages was not the result of scientific observation and inference, but a theory developed to satisfy a theological need, the need for the dissemination of the divine spirit throughout the body.

Perhaps the most entertaining part of this book has no relation to medicine, but consists of a translation of those parts of a Latin edition of *Ptolemy's Geography* into which the editor, Servetus, inserted his own views in an attempt to bring the second-century work up to date. This edition, prepared in 1535, contains further evidence of Servetus's lack of tact, for his remarks on various nationalities are not at all conciliatory. Though he admits that Scots are of quick intelligence and brave in war, he finds that they rejoice in falsehood. The Irish, he says, are inhospitable and cruel. These are surprising charges, but not nearly as severe as some he makes against the inhabitants of some parts of Germany. Sometimes, there is a remark which still holds good. For example, he says that the "language of the English is very difficult to understand and to speak". Again "the French are vivacious, animated and prone to conviviality"; in France, "many eat fowl even though it be very expensive"; in Germany "rarely does one deceive another in business"; the Germans "once imbued with opinions are not easily changed".

Lastly, a dangerous statement in an age of monarchy: "I myself have seen the king touch many attacked by this ailment (scrofula) but I have never seen any cured".

The monograph, taken in conjunction with the modern biographies of the "hunted heretic," will enhance the reawakened interest in this lively and unorthodox sixteenth century figure, whose place in medicine is secure though unusual.

MEDICAL ECONOMICS

THE NATIONAL HEALTH SERVICE IN GREAT BRITAIN*

JACQUES GENEST, M.D., F.A.C.P., F.R.C.P.,† *Montreal*

I AM GREATLY HONOURED by the invitation of the Chairman of your Post-Graduate Medical Board, Dr. MacKenzie, to address you on the subject. This talk on the National Health Service in Great Britain is based upon the experience of two sojourns of a total of five months in England and Scotland between 1951 and 1953. During one of these stays, I visited all the main medical centres and worked in the wards and out-patient departments of two London hospitals.

There is obviously a great deal of passion and prejudice about the NHS in England and when I was sent in 1951 to Europe by the government of this province I tried to study the NHS as objectively as one could, applying the same scientific criteria of observation, precision and critical sense as would be necessary in clinical research. In any appreciation of the NHS by an outside observer, it is often difficult, if not impossible, to distinguish features of the NHS *per se* from those of the previous state of medicine in England or resulting from the general progress of medical care. We must not only judge the NHS against the background of the previous state of medical care and of medicine in England; but also in relation to the best medical care, the best medical practice and the best medical research that we can find elsewhere in the world.

Socialized medicine consists in the nation-wide distribution of the expenses for medical care with the intention of giving the best medical service, both preventive and curative, irrespective of the individual's income. This implies obligatory health insurance, nationalization of hospitals and public health services, with the members of the medical profession as functioning government officials within the plan. This is essentially what the NHS is. It was adopted by an Act of Parliament in 1946,[1] and on July 5, 1948 the Ministry

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of Health took over the administration of the hospitals of the whole country.

Factors responsible for the NHS.—How did Great Britain reach this stage? There are many factors involved both immediate and remote. The Local Government Act of 1929 modifying the Poor-Law Hospital Act of 1601 by giving to the County Councils responsibility for the provision of general beds for the sick resulted in a considerable growth of the hospital system. This factor, plus the development of the voluntary hospitals and the Insurance Act of 1911 were responsible for the fact that in 1938 the Government controlled and paid for half of the total number of hospital beds in Great Britain and, in the same year, 20 million people carried insurance for complete medical care.

During the 1939 war there emerged a strong feeling of oneness and equality in the sacrifices and ordeals of the whole community. Due to the emergency almost every public service came under government control, including all of the hospitals which were integrated and controlled by a central committee in London. Many physicians were put on full-time employment in the hospitals and the greatest number of patients' bills were paid by the Government, since most of the patients were people wounded during the bombings or were military personnel. Very few voluntary hospitals could have remained in operation without annual subsidies from the Ministry of Health. This reached the point that in 1945 and 1946, 90 to 95% of the annual budget of all hospitals in England came in one way or another from government sources. This very high figure was an argument used by Mr. Bevan that the British population should have an NHS and made him decide to seek its approval by Parliament, despite the opposition of the medical profession.

Furthermore the war brought heavier taxation and a marked impoverishment of the general population which made the workers more insistent in their demand for a free complete medical care. The poor working conditions, the low wages and the inadequate medical care in a number of industries or industrial areas were responsible, as in other countries, for the emergence and strength of the workers' unions and of the Labour Party which made a free health service one of the bases of their political platform.

In 1941 the coalition government of Mr. Churchill appointed a Committee headed by Sir William Beveridge to study reconstruction problems related to social insurance and to make recommendations to provide full freedom from want. Sir William pointed out in his report[2] in 1942 three basic requirements for the success of his plan to provide complete security for the British people. The first of these was children's allowances. On page 154, the report states that: "with the present rate of reproduction, the British race cannot continue." The second prerequisite was the maintenance of full employment, and the third was a national health service providing complete free medical care and including the prevention and cure of diseases and restoration of capacity for work. If one adds up all these factors, it becomes easy to understand how socialized medicine came to being in Great Britain.

The British people are one of the most disciplined and politically mature in the world and the English social structure is a very well defined one. No other country could lend itself so well to such a big experiment!

DESCRIPTION OF THE NATIONAL HEALTH SERVICE[3]

The National Health Service is under the control of the Minister of Health, who is advised by a central health services council made up of 41 persons, 35 of whom are appointed by the Minister himself, selected from the various groups dealing with the care of the sick. The NHS is administered by the civil servants of Whitehall—this is important to remember—and is divided into three sections. The first one is the hospital services, the second is the medical practice services and the third is public health.

The hospital services control all the hospitals in Great Britain with the exception of a very few denominational hospitals. The whole country is divided into 14 regions arranged around one or more medical schools and administered by the regional hospital boards. These regional boards, 25% of whose membership are physicians, are responsible for all consultants' and registrars' appointments in the hospitals. Each hospital in turn is controlled by a hospital management committee. The 36 teaching hospitals are under the control of boards of governors which are independent of the regional hospital boards. Each hospital must submit in September its budget for the year commencing the following March and must return to the Treasury any unspent money. This makes planning extremely difficult and complicated and invariably results in the complete expenditure of all funds in order to avoid a smaller allocation the following year. The hospitals' expenditures represented in 1949-1950 more than half the expenditures of the whole NHS or 650 million dollars, of which 60% went into salaries and wages.

To the second section of the medical practices committee belongs the general practice of medicine which includes the general practitioner, the dentist, the oculist and the druggist. This section controlled by 163 local executive councils, which succeeded the national insurance committees, is responsible for personal medical services. There are at present in Great Britain about 19,000 physicians for a population of 45 millions which is a proportion of one physician per 2,300 people.

In the third section of the public health service we find the health centres, the various clinics for pre-natal and post-natal care, for school children,

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for vaccination, for immunization, for tuberculosis and for rehabilitation.

At the present time it should be pointed out that the medical services are not entirely free since the patient has to make a weekly contribution to the national insurance system and has to pay a certain fraction of the cost of the prescriptions, dentures, glasses, trusses and other medical accessories. About 95% of the medical profession receive their income through government cheques. Almost all the hospitals and sanatoria belong to the government and the whole NHS is ultimately controlled by civil servants of the Ministry of Health. It is estimated that about 92 to 95% of the population in England is now under the national health service.

If one takes into account the magnitude of the social change, the transition from the previous state of medicine in England to the NHS has been fairly smooth. This is a tribute to the maturity and sense of discipline of the British people. It is even more a tribute to the sense of social responsibility of the medical profession that the whole scheme did not break down completely. Nevertheless, many of the difficulties encountered since the NHS came into operation are derived from its almost overnight application to the whole country and to all the aspects of medical care. The transition was too hasty and did not allow enough time for the establishment of the huge administrative, advisory and judicial machine necessary for the efficient operation of the system. Furthermore, its enforcement was ill-timed in view of the financial crisis through which England has been going since the war. Finally, the cost estimates for the NHS were grossly underestimated by 3 and even 4 times too little!

COST OF THE NATIONAL HEALTH SERVICE

The individual weekly contribution to the national insurance system varies between 35 cents for an unemployed person under 18 to $1.25 for a worker whose employer pays half of this amount. Less than 10% of the total contributions to the national insurance system or about $100 million went to the division of the NHS in the years 1950-51. Since the total cost of the NHS in those years was 1.2 billion dollars, it means that 92% of the total cost of the NHS had to come from general taxation moneys. This represents about 3.5% of the total government revenue, about 22% of the expenses of the national insurance system and about $27.00 per head of population.

One of the cornerstones of the NHS was intended to be the creation of health centres throughout the country. At the present time, because of the lack of money and the enormous cost of the other services, it has only been possible to build one or two. Each of these centres which would provide general medical, dental and public health services for a population of about 20,000 persons under the local health branch of the NHS would cost about $450,000.[3] Such a centre would include six general practitioners, two dentists and one or two health officers. On this basis, greater London alone would need about 450 such centres.

PAYMENT OF GENERAL PRACTITIONERS UNDER THE NEW REGULATIONS OF 1952

Since the report of the Working Party[4] in 1952, the maximum number of patients allowed to a single practitioner is 3,500 for which he receives an average of 19s. 10d., or $2.73. This represents a total income of $9,800 a year. The average annual payment per patient under the new regulations varies between 17s. and 23s. 8d., depending on the number of patients. In addition the general practitioner receives money for mileage made in visiting his patients, the supervision and delivery of pregnant women, the treatment of temporary residents and from the few remaining private patients. The general practitioners are allowed a 35% deduction from their gross income for income tax purposes. The total amount of money of the central pool for the payment of the general practitioners is about $140,000,000.

PAYMENT OF HOUSE STAFF AND CONSULTANTS (SPENS' REPORT)[5]

The senior house officers receive $1,700.00 a year. The junior registrars, who correspond to our assistant residents, receive from $1,900 to $2,250 per year and the senior registrars and first assistants receive from $2,500 to $3,400 per year. After a senior registrar has been appointed, at the age of 32, to a specialist's post, he receives $4,200 per year with an annual increment of $350 until he receives a maximum of $7,000 per year. In addition there are the special awards given to individual specialists selected by a national committee on the basis of outstanding distinction or for special contributions to medicine. The first award given to 20% of the total number of specialists is $1,400; an additional 10% more receive the second award which is $4,200 per year and another 4% receive the highest award of $7,000 so that the maximum annual income made by a specialist or a professor is now $14,000.

But a specialist may give his services only part-time to the NHS and since the working week is divided on the basis of 11 half days, the part-time specialist is paid a fraction of 11 equivalent to the number of half days he gives to the Service. The payment is made on the assumption that if engaged whole time the specialist would receive $7,000. These part-time specialists are also eligible for the special awards. Like the general practitioners, the specialists are entitled to allowances for car expenses and travel expenses. In addition they receive $11.75 for each domiciliary visit done at the request of a general practitioner. In 1950 there was an average of eight domiciliary visits per consultant per month.

THE GOOD POINTS OF THE NHS

Once more I wish to emphasize that some of my observations on the good or the weak points of the NHS may not represent entirely the effects of the NHS as much as they may reflect conditions of the previous state of British medicine or of the general trends of modern medical care.

(a) The main part of medical research in England depends on the Medical Research Council[6] which is a government body, free of political influence up to the present. The MRC has one large establishment for basic research, the National Institute for Medical Research at Mill Hill, near London. There are now about 90 research workers in the various divisions of the basic medical sciences. In addition the MRC supports 18 clinical units in various teaching hospitals and universities. These units may become more numerous in the future because of the increased interest in clinical investigation in recent years and because of this year's report[7] on clinical research in relation to the NHS. The characteristics of medical research in England are that the greatest part of the funds available come from one central body which is the MRC, that most of the work done under its grants is of good to superior quality and, finally, that there is a minimum of useless duplication. Another important source of money for research is the Nuffield Foundation whose role has become increasingly important and which has rendered eminent service to the progress of medicine in Great Britain.

(b) Medical care costs very little to the individual and there is no question that the public, in general, is satisfied. On the other hand it should be noted that the public is quite ignorant about medicine and often cannot discuss the *quality* of the care received in a general hospital or from general practice.

(c) The previously full time physicians in the hospitals (anæsthetists, pathologists, radiologists, bacteriologists, bio-chemists and also the house staff) receive a better income than before and are given the importance they deserve. Many of them are happy about the change.

(d) The out-patient departments are given greater importance and better organization.

(e) In 1948, there were 6.7 million people over 60 years of age and 4.6 million above 65 years of age. The problem of the care of the old people is one of the major difficulties of the present time in England, as in many other countries. Under the ægis of Dr. Sheldon of Wolverhampton who made a remarkable study of this question, under a Nuffield Foundation grant, the suggestion has been put forward of reserving one flat for old couples out of each six or seven units in new housing projects with the view that neighbours will help to care for these old people and will take a load off the hospitals and government bodies. This return to the Christian idea of brotherly love and charity would save the country a considerable amount of money. Nevertheless at the present time the aged and the chronically sick are poorly provided for.

(f) The most competent section of the medical profession, professors, consultants and top research workers are given more importance than formerly in the advisory committees, in the organization and the development of the service.

(g) Since the Danckwerts Awards[8] and the Working Party Report[4] many general practitioners are now happier about their financial status. Everything taken into consideration, it appears that the British doctors have a reasonable income in comparison with the rest of English society. Most of the practitioners are happier in the sense that they are able to treat their patients free from the inhibitory consideration of the patients' ability to pay.

WEAK POINTS OF THE NHS

(a) One of the most important failures of the NHS lies in its artificial administrative division into the three branches of the hospital services, general medical services, and public health, without any integration at any level. There is very little relationship between the consultant in the hospitals, the general practitioner and the public health officer. This often leads to misunderstanding and mutual ignorance and has dissociated the preventive from the curative aspect of medicine. In the end it is the patient who suffers in this artificial no man's land between the three divisions. His admission to the hospital often constitutes a complete break with his family doctor (who cannot practise in the hospitals). This is also illustrated by the failure of many hospital workers to notify the practitioner of the fate of his patients

(b) Animal experimentation is under the control of the civil servants of the Home Office, who sometimes have little or no knowledge of hospital problems, medical care or of medical research. Any experimentation involving the use of animals requires a written application to the Home Office. Permission is usually given without difficulty but there are exceptions. One of my British friends who is recognized as one of the best surgeons in London, applied for permission to use dogs for experimental cardiac surgery. It took nearly six months of letters, calls and visits to convince the representatives of the Home Office of the necessity of experimenting on dogs' hearts before doing any human surgery. Nevertheless, he was forbidden to do any dog experimentation involving the study of cardiac arrest and resuscitation.

(c) Despite the fact that the patient can choose his own panel doctor he has many difficulties in seeing the specialist he wants or in being admitted to the hospital of his choice, especially in cases of emergency. If a patient is advised by his panel doctor to see a specialist

he must have a written letter for the specialist in question and must go to the hospital where the specialist practices. An appointment at a specialist's out-patient clinic usually involves a delay of two to four weeks. In the out-patient department the patient usually waits from two to four hours before being seen by the specialist, or more often by an assistant or a registrar, since the specialist is required to see only 12 patients per half-day session. He must then return to the hospital for his various tests and x-ray examinations. Finally, he returns for his diagnosis or his treatment, for which in the latter case he is referred back to his family doctor.

Having seen how this is organized there is no doubt in my mind that there is a considerable delay involved in the consultations and enormous loss of man-power hours. The patient often becomes, for the hospital or the consultant, a mere case.

(d) The private charitable and the voluntary welfare associations have been choked and replaced by the cold, slow and impersonal machinery of the various government bodies.

(e) The cost of the NHS has been staggering and explains many of the financial difficulties that Great Britain has had in the last five years. Instead of the original estimates by the experts of the Ministry of Health of 440 million dollars per year, a ceiling had to be ordered in 1950 by the Chancellor of the Exchequer at 1.2 billion dollars per year in order to avoid disruption of the entire national budget. This is almost three times the estimated figure. Even with this, so little money is given to universities and teaching hospitals that they cannot improve their physical standards and increase their research facilities. What moneys are available are subjected to an excessive detailed and inhibitory financial control by the government.

For any expenditure involving more than $2,800, the hospitals need the approval of the Ministry of Health. So far there has been no money available for the re-building of old dilapidated hospitals, like Guy's in London, or for the building of new hospitals and the health centres which are so badly needed. It is recognized that hospital buildings and equipment in England are obsolete compared to ours. In the present political and social situation in England, housing projects and industrial expansion are given priority over the development of hospital facilities.

(f) Since the actual number of young physicians prepared for consultants' posts is too great (there are about three applications per post) there is strong competition for these, as well as competition between consultants for the special awards, with all the unwelcome features attendant on these struggles.

(g) Because of the number of certificates required and the impersonal character of hospital care, professional secrecy and discretion are in many instances things of the past.

(h) Surgeons are paid by operating sessions and receive the same payment whether they do one appendectomy per operating session or four gastrectomies. Many surgeons still cannot admit that the anæsthetists whom they formerly regarded as glorified technicians should now be accorded the same importance in the NHS as they and receive the same salary.

(i) *General practice.*—A recent issue of the *British Medical Journal*[9] devoted to a survey of general practice under the NHS is most interesting. It confirms many of the impressions I received from my two sojourns in Great Britain. For a good number of general practitioners morale, incentive and enthusiasm for work have considerably decreased. This is far from the aim of the Beveridge Report, in which it was a guiding principle that: "The State in organizing security should not stifle incentive, opportunity and responsibility." The general practitioner has no stimulus, such as special awards, to improve his status and his services to his patients outside of his sense of duty which, in general, remains high. He has lost all hospital connections and since he is not paid for minor surgery he refers all such cases to the hospitals to the detriment of his ability and experience.

There is a definite tendency on the part of the public to consider the general practitioner as a person giving certificates and prescriptions and referring to a specialist or a hospital any illness of more than a minor nature. His loyalty is often divided between his own interest in retaining his panel patients wishing certificates for absence from work for trivial complaints and his own responsibility towards his government employers and the common good.

In many instances he is reluctant to take on his panel old people, invalids and the chronically sick because this means much more work and more home calls for the same annual salary. Thus, the general practitioner tends, because of the capitation fee system, to take as many healthy "patients" as possible. He is allowed on his panel a maximum of 3,500 persons. It has been calculated that a physician with this many patients must see an average of 50 to 63 patients per working day of 8 hours. This means 6 to 8 patients per hour or an average of 8 to 10 minutes per patient. This is incompatible with any form of careful examination and with good quality medical care. It leaves no time for the physician to become acquainted with the social and emotional aspects of his patient. It is to the credit of the physician that, unlike union workers, he has a working day of 10 to 14 hours. Even so, with so little time, the general practitioners have a tendency to refer many patients to hospitals for trivial reasons or for the sake of saving the trouble of examining the patients. It is of interest to cite Dr. Hadfield who states in

his recent survey on general practice for the British Medical Association: "I was surprised at the prevalence of the method of examining the abdomen through the clothes and with the patient standing." About 75% of the country doctors and 59% of the town doctors would prefer panels of less than 3,000 patients.

With a ratio of one doctor per 2,300 persons and with the allowed maximum of 3,500 persons per general practitioner, it is very hard for a young doctor to get started except in underdoctored areas, or as assistant to other practitioners, or in the army or colonial service. The situation is so acute that a good number have preferred to emigrate. Before starting practice the young doctor must have the consent of the medical practices committee.

The field of action of the general practitioner has been restricted by the various public health clinics. Often there is no collaboration, in fact there may be antagonism between the general practitioner and the public health officer or even the hospitals' medical officers. Almost everywhere he has been completely eliminated from the hospitals. He feels isolated and, very often, has no chance to meet the consultant to whom he refers his patients.

(j) In the care of the aged, tuberculous patients, the chronically sick, the infirm and the patients with infected tonsils the situation is so bad that there is a waiting period of nonurgent cases of 6 months to 2 years before admission to the hospital and during that time the patient becomes a burden on the general practitioner. In some instances it has been said and written[10] that the waiting period of presumed tumour cases is about three months. Many hospital wards are closed because of shortage of nurses.

(k) A statistical report entitled *The Social Services, Needs and Means,* published in 1952 by MacLeod and Powell, members of the Conservative party, shows that in 1951 there were proportionately more people receiving help from public welfare than in 1900 despite the national insurance system and the Beveridge plan which was supposed to guarantee complete security from cradle to grave.

In summary, the main weaknesses of the NHS consist of:

(a) the lack of unity and of integration between the three divisions of general practice, public health, hospital services and consultants;

(b) the excessive demands for services of the general practitioners which render them unable to give the necessary time to cases which deserve close attention;

(c) the isolation of the general practitioners from hospitals, the long waiting list in all hospitals for nonurgent cases, and the lack of facilities for the aged, chronically sick or tuberculous patients.

There are of course many other points that could be brought up in relation to the NHS. I could also mention the intense irritation and frustration felt by the leaders of the medical profession when debating with civil servants on the day-to-day administration of the medical and hospital problems or on developments of the Service.

Because of the sense of compromise, the discipline and the maturity of the British people and because of their social insurance system I have the impression that the NHS will work. The British have embarked upon a big socialist experiment but, as they have done in recent years, they will continue to adapt and improve it progressively and, when the international situation permits a decrease in defense expenditures it is likely that on the whole the British people will have a satisfactory total medical care, provided the ideals of the medical profession are not choked by excessive and inhibitory administration or by loss of incentive and enthusiasm.

The NHS may turn out to be of great advantage to the welfare of Britain, but to establish in Canada a health service like the NHS is I think out of the question in view of the economic, political and social differences between the two countries. We will have to wait another decade to evaluate the British experiment and I am not ready, by far, to advocate a similar transformation of our present system which provides the people, on the whole, with better medical care. There are many good points to take from the British experiment. We must take advantage of them but we must create a system that will suit our conditions best.

Social medicine is a field where passion, prejudice and wishful thinking are easily given free play. Total security for the individual may never exist in our world. Without the old virtue of thrift and without faith, any system devised to give complete security and freedom from want is bound to be incomplete and seriously deficient. I sincerely hope that in Canada the changes that will come will be derived from an objective, careful study of all the aspects of the problems involved and by progressive steps.

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MEDICO-LEGAL

HINDSIGHT

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INFREQUENTLY the Canadian Medical Protective Association is called upon to assist a member in a case where the fact of an ill result is indubitable but where the reason for the ill result, whether carelessness in a legal sense or an unavoidable accident, is in great doubt. The doubt may extend to the doctor himself. In the light of subsequent knowledge—and only as a result of that knowledge—he may come wrongly to the conclusion that he was guilty of an error in judgment sufficiently serious to render him culpable.

Early in 1952 a reputable, highly respected surgeon had referred to him a patient with "a well advanced Dupuytren's contracture of the left hand involving a ring finger with puckering of the skin". There was, in addition, lesser involvement of the right hand, the sole of the right foot and the sole of the left foot. It was judged wise to undertake repair of the left hand at once. The patient was anxious that operation be performed over a week-end so that it might interfere as little as possible with his work. Accordingly, after admission to a hospital, on a Saturday morning the surgeon undertook a subcutaneous fasciotomy.

For the operation short, thin and narrow scalpel blades were used. Another surgeon, previously, had broken a number of similar blades in the hospital so that, although the surgeon was unaware of the fact, only two blades were available at the time of operation. Those two were broken before the operation was complete.

When the surgeon learned that there were no more small blades he was faced with the difficult choice of either stopping the operation or proceeding with another, less suitable blade. Having in mind the patient's hope that the operation would interfere as little as possible with his work, the surgeon elected to use a slightly larger blade, one-quarter of an inch in width instead of about one-eighth inch, more rigid and heavier. "In attempting to complete the division of the fascia I suddenly noticed that the finger straightened freely . . . the next day when I asked him to move his hand I found that he had no flexor power in this finger. . . ."

A consultation was held and it was decided that the severed tendon should be repaired by someone who did a considerable amount of tendon surgery. As well, the surgeon was leaving to go abroad and in any event would have had to refer the patient to another surgeon for subsequent care. The second surgeon attempted a repair and was unsuccessful.

Some months later the first surgeon requested the patient to let him see the finger so that he might judge progress. There was discussion about the result of the operation and, for the first time, the patient suggested that he was entitled to damages for the injury. The doctor, quite properly at that time, refused to discuss this aspect of the matter. Some time later the surgeon received a lawyer's letter asking for damages. At that stage the Association placed the conduct of the case in the hands of its solicitors.

It was recognized that the surgeon had been faced during the operation with a difficult choice and it was realized that his decision was made with the operative needs and possibilities in mind, influenced as well by the patient's clearly stated desire that the operation should mean as little time as possible away from work. It was assumed that the surgeon would be prepared to defend his decision although the result had been poorer than he or the patient expected.

However, in retrospect, the surgeon had reached the conclusion that, without the proper scalpels, he should have refused to finish the operation. He felt he had made an error in judgment because he allowed himself to be unduly influenced by the patient's extreme desire to return to work as soon as possible. Persuaded therefore that his judgment had been bad the surgeon was unwilling to defend himself and a settlement had to be made. An amount of $1,700 was agreed upon between the two parties, releases were obtained and the matter was closed.

This case illustrates a not uncommon dilemma. Faced with unexpected complications, complications that could not have been foreseen, doctors must weigh new facts, must make new decisions with no time for reflection, must choose one of several courses of action and follow it immediately. As a result of subsequent developments it becomes apparent that the course of action chosen was not the best, that another would have been better. With complete but new and previously unavailable information it is easy to know what should have been done. Hindsight is always better than foresight.

How then should the doctor act when he is called to legal account for such an error of judgment? He should remember that his decision was made carefully, that he possessed adequate knowledge and to the best of his own ability used it in the light of the then knowledge of the facts. He may have to regret the result, and if it was poor he undoubtedly will, but he need not accept blame for a poor result his best judgment could not prevent. Remembering that the courts do not expect of doctors any more than of anyone else that all their results shall be good, remembering that as long as he had adequate knowledge and used it with reasonable care and skill he will not be held culpable, the doctor, therefore, when a legal action is brought against him as a result of the error, should be prepared to defend himself. To do otherwise is to harm himself and the other members of the profession in his district.

*Secretary-Treasurer, Canadian Medical Protective Association.

Association Notes

THE CANADIAN ASSOCIATION OF RADIOLOGISTS

Council Meeting: 9.30 a.m., Tuesday, June 15.
Special General Meeting: 2.30 p.m., Tuesday, June 15.
Place: Board Room, Academy of Medicine Building, 1807 W. 10th Avenue, Vancouver.

CANADIAN NEUROLOGICAL SOCIETY

Sixth Annual Meeting, June 19 to 21, 1954, Vancouver.

All physicians interested in this programme are welcomed to the scientific sessions.

Saturday, June 19:

9.00 a.m.—Registration: Meeting of Council.

10.00 a.m. - 1.00 p.m.—Scientific Session.

Prenatal malformations of the C.N.S. of established etiology, A. S. Dekaban.
Spinal cord tumours in the newborn, Dwight Parkinson; Harry Medovy; J. R. Mitchell.
Intramedullary spinal cord tumours, A. M. Hudson; J. C. Richardson.
Hereditary sensory neuropathy, Irving H. Heller; Preston Robb.
A clinical syndrome associated with ruptured aneurisms of the anterior communicating artery, J. W. Cluff.

2.00 - 4.00 p.m.—Scientific Session.

Microscopic observations of the pial vessels, John E. Harvey.
Present concepts of the pathogenesis and immunology of poliomyelitis, A. J. Rhodes.
Neurological aspects of poliomyelitis, Harold V. Rice.

4.00 - 4.30—Business Meeting.

Monday, June 21:

9.00 a.m. - 12.45 p.m.—Scientific Session.

The effect of large fat meals on the viscosity of the blood, Roy L. Swank.
Commentaries, slides and moving pictures: "An automatic injector for angiography", Jean Sirois.
Current concepts of the body-image, J. R. Smythies.
The cingulate gyrus in relation to consciousness, Margaret Kennard.
Axon terminals in the human cerebrum and cerebellum, Wm. C. Gibson.
Cerebral anoxia and hypoglycæmia, P. M. Heywood; J. C. Richardson.
Copper metabolism in cirrhosis of the liver, J. L. Silversides.

2.00 p.m. - 4.30 p.m.—Symposium on Head Injuries.

Acute subdural and intracerebral hæmatoma with some thoughts on carotid arteriography in acute head injuries, Chas. G. Drake.
Subdural hæmatoma, Wm. S. Keith.
Neurological and psychiatric aspects of accidental head injuries and their complications in children, J. L. Desrochers; Wanda Shiffmann.
Conclusion: Clinical and medico-legal discussion, Jean Saucier.
Differentiation of the sequelæ of head injury, C. E. G. Gould.
Discussion: Frank Turnbull; Allan Bailey.

4.30 p.m.—Business Meeting.

MISCELLANY

OSLER SOCIETY ANNUAL DINNER

Sir Russell Brain, President of the Royal College of Physicians of England, Physician to the London Hospital and various other hospitals in London, Eng., was the guest speaker at the Annual Dinner of the Osler Society of McGill University held on March 30, 1954, in the Ritz Carlton Hotel, Montreal. He was introduced by Dr. Wilder Penfield who recalled that Sir Russell and he had been undergraduates at Oxford University at the same time, and mentioned the main stages in the career of the guest speaker.

Sir Russell Brain had chosen as the subject of his speech "Words." Remarking that his own approach to the subject of language was primarily neurological and that in all other aspects he was an amateur, the speaker emphasized that everything which distinguished man from the higher apes involved the use of words. It was of great interest to speculate on how the original anthropoid ape came to discover the use of words. Study of this question, which had involved a decisive step in the progress of the animal kingdom, was complicated by the fact that no animal appeared to be acquiring the power of speech at present.

Four theories had been propounded of the origin of speech. They were referred to by Müller as the ding-dong theory (words first associated with meanings), the bow-wow theory (onomatopœia), the pooh-pooh theory (interjections of emotional significance) and the yo-heave-ho theory (words being at first sounds associated with communal physical effort).

Language had from the first been associated with emotion. The decisive step was taken when words ceased to be used solely to indicate something present, such as a lion, and became symbols of an absent object. Words, said the speaker, enabled us to talk about things in their absence, and the first ape to use words was in fact the first man.

Sir Russell Brain dealt at some length with the question of speech and handedness. There was an obvious advantage in having the speech centre in one cerebral hemisphere, but why should it be on the left? It was clear that the acquisition of speech was not the cause of handedness, since there were righthanded and lefthanded chimpanzees (in about equal proportions).

A curious feature of words was that the cortical stimulus evoked by a word was not affected by the many ways in which it could be said. Sir Russell Brain mentioned a type of telephone which had been invented, in which a filtering system robbed words heard through the earpiece of all their emotional association. It had been suggested that a similar filtering mechanism existed in the cerebral cortex. This led to a consideration of the wide separation between the propositional speech of Hughlings Jackson (speech designed to make a statement of fact), intended to stimulate the cerebral cortex, and speech intended to arouse emotion by stimulating the diencephalon. This separation was seen in some cases of aphasia, in which for example the patient could swear although he would not answer questions.

Poetry gave the best example of the use of words to excite emotion. Because of this, a poem could not be expected to have a meaning in the scientific sense any more than a piece of music would, nor could it be translated or paraphrased. After drawing upon the Bible for examples of the use of prose to excite emotion, Sir Russell contrasted a poem "Wingéd Chariot" by Walter de la Mare with some verse by Dylan Thomas, to show the superficial difference and the deep similarity between so-called modern poetry and the conventional type of verse. The difference was really that a modernist like Dylan Thomas went beyond the conventions to which the reader was accustomed in the use of words, while the older poet did not.

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Laughter and humour were discussed at some length by the speaker. The impact of the pun, which was the simplest form of verbal humour, had been explained by Hughlings Jackson on the basis of a verbal diplopia. This element of diplopia, on which the radio largely depended for humour, was present in other forms of wit. *Double entendre* had of course an emotional significance as well.

The extent to which thought depended on words was worthy of consideration. If there was a close dependency, then words could quite clearly lead thought astray, as they might well have done in some philosophical problems. There was a close physical relation between thought and words. For example, the child spoke its throughts aloud quite as a matter of course, and the adult might use spoken words as an aid to thought in similar fashion. The nervous processes underlying ideas resembled those underlying words; ideas might be said to be complicated words.

In conclusion, Sir Russell Brain drew attention to the current view that all human behaviour might be "scientifically" explained in terms of neurophysiology. Was this true, or was science not the only way of describing the world? The question, said Sir Russell, was whether humanity would survive if it continued to develop the language of the cerebral cortex at the expense of the language of the whole man.

The speaker was thanked by the organizer of the Dinner, Mr. Thomas J. Sullivan, Jr., and it is pleasing to record that Mr. Sullivan's brief speech was of a quality worthy of the occasion.

WHO EXPERT COMMITTEE ON ALCOHOL*

This newly formed WHO Expert Committee must be distinguished from the Alcoholism Subcommittee. The new committee is concerned only with the physiological, pharmacological and biochemical properties of alcohol. It defines tolerance to alcohol as the capacity of the organism to function with alcohol in the blood without measurable deterioration in nervous function, and lays stress on the wide individual variations in human tolerance, and on the possibility of acquired increase in tolerance, a phenomenon requiring basic research. It feels that a sharp distinction must be made between the transient and usually harmless symptoms due to withdrawal of alcohol and those produced by morphine withdrawal. It considers alcohol as "a drug whose pharmacological action is intermediate in kind and degree between addiction-producing and habit-forming drugs, so that compulsive craving and dependence can develop in those individuals whose make-up leads them to seek and find an escape in alcohol. With this substance the personal make-up is the determining factor but the pharmacological action plays a significant role. Damage to the individual may develop, but does so in only a minority of users. The social damage that arises extends, however, beyond these individuals themselves."

The approach to study of alcoholism by animal experiments, the metabolism of alcohol, and the problem of alcohol and traffic were studied. Scientifically planned studies of the role of alcohol in road accidents should be encouraged, but the problem must, for the present, be attacked on a national level.

*World Health Organization Technical Report Series No. 84.

MEDICAL SOCIETIES

CANADIAN PSYCHOANALYTIC SOCIETY

Scientific Meeting (Montreal, April 29, 1954). A paper was delivered by Dr. Jean-Pierre Labrecque: "On Transference and Counter-Transference."

A clinical case was presented, which showed how counter-transference phenomena may interfere in a psychoanalytic treatment, by encouraging the analyzand's resistances to transference manifestations.

J. B. BOULANGER

C.M.A. QUEBEC DIVISION

The Annual Meeting of the Quebec Division of the C.M.A. was held at Three Rivers on May 7 and 8, under the Presidency of Dr. R. Lemieux of Quebec. The weather was merciful enough and there was a very encouraging attendance. The first day was spent on scientific programme which included papers by Dr. Louis Frenette of Grand'Mère, Dr. Adrien Paradis of Shawinigan Falls, with Dr. Kenneth Warren of the Lahey Clinic, Dr. Samuel Cosgrove of Columbia University and Dr. Roy Farquharson of Toronto. Later, Drs. C. E. Lamoureux and L. Letienne of Three Rivers spoke on Intra-Medullary Nailing of the Femur and Dr. R. St. Pierre on Pulmonary Hypertension.

On Saturday morning, five short papers were read on various non-surgical aspects of cancer. With Dr. J. A. Denoncourt of Three Rivers in the chair, Dr. A. Cantero spoke on Research, Dr. Phoebe Cox on the Radioactive Isotopes, Dr. Allen Gold on Endocrines in Cancer, Dr. L. L. C. Simard on the Delay in Cancer Diagnosis, and Dr. J. Bouchard on Radiotherapy.

The most exciting part of the programme was as usual the clinicopathological conference on Saturday afternoon, in which Drs. J. Olivier and G. Copping both came as near as was humanly possible to an exact diagnosis of the case of pulmonary carcinoma whose history was available.

The meeting was closed by the new President, Dr. A. Tétreault of Three Rivers; the President-elect is Dr. A. Powers of Hull.

In an excellent series of scientific exhibits ranging from kits for treatment of poisoning to parasites, the highlight was perhaps the alarming display of sport injuries, which added point to the dictum of Professor J. B. S. Haldane "whenever I feel an urge to take exercise, I lie down quickly and I find that it soon passes off."

The meeting fully reflected the careful preparations which had been made for it and the annual banquet and entertainment will remain as a very pleasant memory to those attending.

QUEBEC ASSOCIATION OF PATHOLOGISTS

The annual meeting of the Quebec Association of Pathologists was held at the Faculty of Medicine of Laval University on April 30 and May 1 last. Seventeen papers were presented by the members of the Association and by visiting members from Ontario. J. C. Patterson was the guest speaker: he discussed the value of the different theories concerning atherosclerosis.

The executive committee for the coming year is made up of Dr. J. L. Riopelle, president, Dr. M. Mackenzie, vice-president and Dr. S. Lauze, secretary-treasurer.

CORRESPONDENCE

CONGENITAL MICROCOLON

To the Editor:

I read with interest the case report entitled "Congenital Microcolon" by Dr. Jules Lavoie which appeared on page 187 in the February issue of the *Canadian Medical Association Journal*. There are a few comments I should like to make concerning some points mentioned in the paper.

Congenital microcolon, by definition, is a congenitally small narrow colon which by itself causes complete or nearly complete intestinal obstruction. It is, indeed, a very rare abnormality and few authenticated cases have ever been reported. A small shrunken colon, however, is almost invariably found distal to an area of intestinal atresia. This so-called "microcolon" is present simply because meconium has not been allowed to pass along through the lumen. This colon is normal in all respects and will enlarge to a normal calibre shortly after effective surgical treatment directed to the proximal area of intestinal atresia. In the case reported by Dr. Lavoie, therefore, the colon should not be termed a "congenital microcolon" but is in fact the small shrunken colon commonly found distal to an area of atresia.

In this situation, Lipiodol or barium given by rectum frequently will not pass up the colon, and as a diagnostic study contrast radiography is so apt to be misleading that it should not be performed except under unusual circumstances. The upside down x-ray film of the abdomen also is only indicated in a case of imperforate anus when valuable information concerning the distance between the blind ending colon and the anal dimple may be obtained. With other intestinal obstructions of the newborn, the upside down film gives only misleading information in that air-distended loops of small bowel may rise up into the pelvis, leading the examiner to the mistaken belief that the distended loop is low in the colon rather than high in the small intestine. To establish a diagnosis of small bowel atresia, only flat and upright x-ray films of the abdomen are required. Information as to the level of the obstruction is obtained by estimating the length of gas-filled intestine visualized in the films.

On examination of the x-ray accompanying the case report in the *Journal*, it can be seen that air distends the stomach, duodenum, and the first inch or two of the jejunum. No air is visualized in the distal intestine, so that from this film a diagnosis of jejunal obstruction can be made. In high intestinal obstructions the proximal intestine is usually kept moderately well decompressed by vomiting, so that abdominal distension is uncommon. The infant in the case reported had a tremendously distended abdomen. Radiography had shown that this was not gaseous distension, so that preoperatively it might have been suspected that the abdomen was distended by intraperitoneal fluid, or by a fluid filled structure such as an intestinal duplication or a distended urinary bladder.

At operation the baby was found to have a distended bladder; three areas of intestinal atresia (one at the ligament of Treitz, one in the mid jejunum, and one in the distal ileum); and a very small malrotated colon. The child had a combination of anomalies exceedingly difficult to treat by surgery. There was, however, nothing to be gained by performing an ileostomy distal to the two areas of jejunal atresia. Confronted with this problem, it is my opinion that the correct surgical approach would have been to perform side-to-side duodenojejunostomy using a jejunal loop distal to the second area of jejunal atresia, with excision of the intervening intestine. In addition, a double-barrelled Mikulicz ileostomy at the site of the ileal atresia could have been constructed. Admittedly this would have left very little proximal intestine for the maintenance of the infant, but the procedures might have been successful in getting him over his immediate difficulties. The spur of the Mikulicz ileostomy could have been crushed within two to three days after operation, following which the ileostomy could have been closed with re-establishment of bowel continuity.

The distended urinary bladder was inadvertently opened, and subsequently closed. If the bladder had been closed around a suprapubic catheter, the bladder obstruction would have been overcome and, if the infant had survived, investigation and treatment of the urethral obstruction could have been carried out at a later date.

The multiple nature of the anomalies in the case reported makes surgical cure improbable, but not impossible. At the Boston Children's Hospital from 1940 through 1952, 88 cases of intestinal atresia were treated with a recovery rate of 53%. Of the 88 infants, four had multiple areas of intestinal atresia, and of these four, two survived.[1]

I realize that it is always easier to diagnose and to treat in retrospect than when one is initially confronted with the actual patient. In any event, I submit the above comments to you to correct one or two statements made in the case report which I believe are misleading, and to point out that surgical treatment in these conditions is not uniformly fatal, but can be performed under favourable circumstances with a survival rate of approximately 50%.

COLIN C. FERGUSON,
Professor of Surgery,
University of Manitoba.

REFERENCE

1. GROSS, R. E.: The Surgery of Infancy and Childhood, W. B. Saunders Co., Philadelphia, p. 163, 1953.

CONGENITAL MICROCOLON

To the Editor:

I thank Dr. Colin C. Ferguson for his interest in my paper on "Congenital Microcolon," but I do not agree with his comments.

1. The congenital microcolon, even small and narrow, is a perfect colon in all respects. In my case report, the colon was not shrunken or collapsed, as Dr. Ferguson says, but normal except for its calibre. It is not true that this "so-called microcolon" was present simply because meconium had not been allowed to pass through the lumen; no meconium passed through the rectum, and the latter had a normal calibre. Moveover, when the right colon alone is affected by this anomaly, the distal colon has a normal calibre too.

2. I would like to know why lipiodol or barium given by rectum would not pass up the colon, if the latter is not a true microcolon but is only shrunken or collapsed and is waiting for something in it to enlarge.

3. A diagnostic study, normally, is made to have a diagnosis. Here, Dr. Ferguson speaks as if we should have known the diagnosis: in that event, no examination would have been necessary. The baby had an enormous abdomen, no meconium passed through the anus and it was impossible to go far with lipiodol through the anal canal; for those reasons, I think we cannot be blamed for having carried out the preoperative diagnosis and that examination; a like examination is made not only in case of imperforate anus but also in case of imperforate colon or rectum, even if the anus is normal.

4. An ileostomy distal to the two areas of jejunal atresia was performed, not as a life-saving measure, but as the only procedure that could be followed to relieve the distension. Those two areas were of the partial type of atresia, what Gross calls "stenosis"; the proof is that the ileostomy discharged meconium until death, even if the bowel distal to the second portion of atresia was

completely emptied during the operation. A side-to-side duodeno-jejunostomy would have been useless, for the case was absolutely hopeless.

5. If we had had one ounce of hope, we would have closed the bladder around a suprapubic catheter, as suggested by Dr. Ferguson; in the circumstances, we thought it was sufficient to leave a urethral catheter.

6. At the Boston Children's Hospital from 1940 through 1952, 88 cases of intestinal atresia were treated with a recovery rate of 53%. Of the 88 infants, six (not four) had multiple areas of intestinal atresia, and of these six, four survived. But Gross, who reports those cases, does not mention one case resembling ours and does not even speak of congenital microcolon, probably because the condition is absolutely hopeless. Until I have proof to the contrary (and Dr. Ferguson did not make that proof), I persist in believing that the surgical treatment of congenital microcolon (I do not say of intestinal atresia) is uniformly fatal.

May I refer also to Dr. Cluny MacPherson's letter in the April issue of the Journal, in which he asks me if I encountered in my search of the literature a case of three consecutive births having microcolons.

I suppose Dr. MacPherson operated on or autopsied the three babies he mentions, because we cannot speak of microcolon without that proof. In any event, I did not find any such cases and I wonder if thyroid insufficiency is a factor in this extraordinary anomaly.

JULES LAVOIE

REFERENCES

1. AIRD, I.: Companion in Surgical Studies, E. & S. Livingstone, Edinburgh, p. 718, 1949.
2. GROSS, R. E.: The Surgery of Infancy and Childhood, W. B. Saunders Co., Philadelphia, p. 163, 1953.
3. ILLINGWORTH, C. F. W. AND DICK, B. M.: J. & A. Churchill Ltd., London, p. 502, 1947.

SPECIAL CORRESPONDENCE

The London Letter

(From our own correspondent)

PAY INCREASES

Increases in remuneration for two sections of the profession have recently been announced. Neither has been received with much enthusiasm. Both awards demonstrate the dreary deadening effect of the apparently endless negotiations which are necessary under a National Health Service in order to persuade a government department that a professional man is just as worthy of his hire as a labourer. Hospital medical staffs, ranging from house officers to consultants, have received increases in remuneration which will cost the country approximately another £3,000,000 annually. This increase is the result of negotiations which have been going on since 1948. The increase to consultants' remuneration is meant to correspond to the so-called Danckwerts award to general practitioners last year.

It is difficult to assess the justice of the award, but it is doubtful whether many share the optimistic view of *The Times* that "this ends, it may be hoped, a prolonged and acrimonious wrangle". Two initial criticisms of the award are that it is not retrospective as was that to general practitioners, and that the practical applications are so vicarious that it has been found necessary to include in the agreement a special clause protecting any individual against losing pay on the coming into operation of the new agreement!

The negotiations over increase in pay for Civil Service doctors have been even more acrimonious, and at one time reached the stage of the British Medical Association refusing to accept advertisements for Civil Service appointments in the *British Medical Journal*. This strong reaction accelerated the process of Government Departments being deprived of the service of the able type of man which they require as their medical officers, and apparently it has only been under such duress that the Treasury has agreed to the increases in pay which have now been announced. These raise the basic rate of pay from the present range of £1250 (at age 35) to a maximum of £1725, to the range £1500-2100.

A NEW HEALTH CENTRE

There has just been opened in the new town of Corby, in Northamptonshire, a new experimental health centre. In 1934, Corby was a small village of 1,500 inhabitants; today it is a town of 20,000 inhabitants and a large steel centre. The nearest hospitals are at Kettering (eight miles) and Northampton (25 miles). The Nuffield Provincial hospitals Trust decided that this was an ideal spot on which to erect an experimental "health centre," especially as there was no likelihood of a hospital being built in Corby for many years to come. The Centre is more accurately described as a "Diagnostic Centre" and provides examination, consulting and treatment rooms for general practitioners and visiting consultants, a small laboratory, a chest clinic, an x-ray department and a physiotherapy department. The general practitioners of Corby will retain their existing surgeries, but will be able to rent the consulting rooms at the Centre to examine their patients requiring fuller examination and investigation, and for consultations with visiting specialists. In later stages a unit of maternity beds and a unit of general-practitioner beds are to be added, as well as local authority clinics. In the words of the Trust, the experiment has "two simple objects: to improve the general practitioners' facilities for giving a good service to their patients; and to see whether—by bringing the specialists to the patients, and into consultation with the general practitioners—the in-patient and out-patient demand on hospitals can be lessened".

CANCER OF THE LUNG

Provisional figures for deaths in England and Wales in 1953, published by the Registrar-General show a further increase in the deaths from cancer of the lung. The provisional 1953 death rates for all forms of cancer are 2,165 and 1,836 per million population for men and women respectively; the 1952 figures were 2,151 and 1,850. The rise in the rate for men includes an increase from 568 to 607 per million population for deaths assigned to cancer of the lung and bronchus, making a total increase since 1947 of 57%. The rate for cancer of the lung and bronchus for women remained steady—99 per million, compared with 98 in 1952. Of the deaths of men dying of cancer (45,924), 28% (12,873) were certified as due to cancer of lung and bronchus. Of the deaths of women from cancer (41,989), only 5% (2,255) were so certified. A more reassuring picture is presented by the figures for respiratory tuberculosis, the total number of deaths from which was 7,911, with a provisional death rate of 179 per million persons. This represents a decrease of 16% from 1952, and 60% from 1947.

FREDERICK BANTING HOUSE

The Duchess of Gloucester recently paid an official visit to the Frederick Banting House. This is the Diabetic Association's memorial to the co-discoverer of insulin, and was opened early in 1953. It takes the form of a house for elderly diabetics, and is situated at Kingston Hill on the southwestern fringe of London. There are 29 residents—all old-age pensioners. Some are bed-ridden, whilst others, although "aged and infirm", are able to be up and about for at least part of the day. The Home has been full to capacity since it was opened. The very success of the Home has raised in an even more acute form the problem of the elderly diabetic which has always been one

of the chief interests of the Diabetic Association. One of the complicating features of the elderly diabetic is that so many homes for the aged and elderly are not prepared to accept him (or her) because of the special diets and extra medical care which are required. The Association is hoping that it may be possible to open other Homes for these unfortunates in the provinces.

London, May 1954. WILLIAM A. R. THOMSON

OBITUARIES

DR. WILLIAM ARRELL, 86, died in Hamilton, Ont., on April 8. A graduate in medicine of the University of Toronto in 1894, he practised in Caledonia for a short time and in Cayuga, Ont., for 14 years. After taking a postgraduate course in New York he returned to Hamilton as an ear, eyes, nose and throat specialist. He retired in 1942.

DR. WILLIAM ALBERT CLARKE of New Westminster, B.C., died on April 7 at the age of 67. Born in Toronto and a graduate in medicine of the University of Toronto in 1910, he practised first in Brock, Sask., and then in Vancouver, B.C. In 1914 he enlisted in the Canadian Medical Corps and served as a major with the Fifth General Hospital at Salonika, Greece. For many years he was physician to the British Columbia Penitentiary, the port of New Westminster and the Canadian Pacific Railway. In 1942 Dr. Clarke re-entered the medical corps and served with the rank of lieutenant-colonel as second-in-command to the Pacific Command medical officer. He was a past president of the British Columbia Medical Association and, in 1920, was one of six doctors awarded the Prince of Good Fellows award. He is survived by his widow and two sons.

DR. C. P. FENWICK, wartime director-general of medical services for the Canadian Army, died at his home in Montreal on March 20 at the age of 62. A native of St. John's, Nfld., he attended London University, Eng., before entering the University of Toronto where he graduated in medicine in 1916. One year later he won the Military Medal while serving with the Canadian Expeditionary Force. After World War I, while in private practice in Toronto, he maintained his connection with the non-permanent active militia. In 1934 he became a lieutenant-colonel and five years later received the Efficiency Decoration. In 1939 Dr. Fenwick went overseas with the first division and his subsequent career saw him in all Canadian theatres of World War II. In his rise to director-general of medical services he was successively assistant director and deputy director, having held the latter position during the invasion of Europe on D-Day. The King honoured him twice for his services, creating him Commander of the British Empire in 1944 and Companion of the Bath in 1946. On his return to Canada, Dr. Fenwick became chief of medical services for the Canadian Pacific Railway. In this position he directed the work of eight district medical officers and 375 part-time medical officers throughout Canada. He continued as a member of the Medical Defence Council and was president of the Defence Medical Association in 1946-47. Dr. Fenwick is survived by his widow and two daughters.

DR. ESLEY R. FROATS died in Yonkers, N.Y., on March 23 at the age of 51. Born in Spencerville, Ont., he graduated from Queen's University. He was attending surgeon and secretary of the medical board of Yonkers Professional Hospital and was past president of the Yonkers Academy of Medicine.

DR. JOSEPH VICTOR GOYETTE of Granby, Que., died on March 14 after a lengthy illness. Born in 1910, he graduated in medicine from the University of Montreal in 1939. Dr. Goyette practised in Granby until 1943 when he took a three-year postgraduate course in surgery at the University of Pennsylvania. On his return he served as surgeon of the Saint Joseph Hospital in Granby until his illness in 1951. Dr. Goyette was founder and past president of the Medical Society of Granby. He is survived by his widow and two children.

DR. CLARENCE HENRY died on March 9 in Shaughnessy Veterans' Hospital, Vancouver. A native of Norwich, Ont., he graduated from McGill University in 1902 and opened his practice in Yorkton, Sask. In World War I he served overseas with No. 8 Saskatchewan Hospital Unit. After the war he remained in Yorkton until 1923 when he went to Regina to become the first practising radiologist in that city. During his years on the prairies, Dr. Henry was health officer at Yorkton and was active in originating milk pasteurization. In 1931 he became the first therapeutist in the Regina cancer clinic where he remained until 1940 when he left to go into private practice in Victoria, B.C. He retired in 1947. He is survived by his widow, three daughters and one son.

DR. BRUNO LAHAYE, 52, died in Quebec, Que., on March 17. Born at St. Zephirin de Yamaska, Que., he graduated in medicine from the University of Montreal. After practising in Nicolet, Que., for eight years he joined the health department and devoted the rest of his life to the problems of public health. He formed one of Canada's first sanitation organizations in Nicolet and, after taking a course in preventive medicine at the University of Toronto, he went on to become medical health officer of the Province of Quebec. A member of many provincial and national medical associations, Dr. Lahaye is survived by his widow, one daughter and one son.

DR. JOHN HENDERSON McFAUL, 91, died in Toronto on April 4. Born near Seaforth, Ont., he graduated from Trinity Medical College. He was the last living member of the class of 1887. Dr. McFaul began his practice in Toronto in 1892 and was on the staff of the Western Hospital when it had its beginning in a house. He continued to practise in Toronto until his retirement in 1934. He is survived by two daughters and one son.

DR. WILLIAM L. ROBINSON, provincial pathologist in Ontario for 40 years, died at Toronto General Hospital on March 26. Born in Portage La Prairie, Man., in 1885, he attended McMaster University and later the University of Toronto where he received his degree in medicine in 1913. For a short time he served as medical officer for construction crews building the railway through the Kettle Valley in the Rocky Mountains. In 1914 he joined the pathology department of the University of Toronto and, apart from service as medical officer at No. 4 Canadian General Hospital in England during World War I, he remained with the department until his death. In addition to his work as professor of pathology at the University of Toronto, associate director of the pathology department and a lecturer in medical jurisprudence, Dr. Robinson was also consulting pathologist to the chief coroner's office, the Toronto General and Sunnybrook Military Hospitals. In the *Noronic* disaster of September, 1949, he played a key role in the work of identifying the victims. He is survived by one son and one daughter.

WILLIAM LIPSETT ROBINSON,
B.A., M.B., F.R.C.S.[C]

AN APPRECIATION

In the passing of Dr. William Robinson, for many years pathologist to the Toronto General Hospital and Professor of Pathology in the University of Toronto, Canadian Medicine has suffered a well-nigh irreparable

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loss. His fame as a histopathologist and his high reputation as an expert in forensic medicine transcended the boundaries of his native Canada; his idealism, his love of his fellow men, his capacity for friendship, and the warmth of his personality, endeared him to all with whom, in the course of a long, busy and useful life, he came in contact. Truly, he exemplified what was said of our profession by Robert Louis Stevenson, "When this stage of man is over and done with, and only remembered to be marvelled at in history, he will be thought to have suffered as little as any from the defects of his period, and most notably exhibited the virtues of his race."

In 1915 he joined the staff of the Department of Pathology of the University of Toronto, then under the direction of the late Professor J. J. Mackenzie. As professor he served the department with, successively, the late Professor Oskar Klotz, Professor William Boyd, and Professor John Hamilton. He retired, owing to ill health, in 1953. During World War I, he served with the Canadian Army Medical Corps, overseas. He was, for some 35 years, Pathologist to the Toronto General Hospital. He was a charter Fellow of the Royal College of Physicians and Surgeons of Canada. He was a past president of the Ontario Association of Pathologists, a member of the Canadian Association of Pathologists, of the American Association of Pathologists and Bacteriologists, and of many other medical and scientific bodies. He was a great pathologist, a great teacher, a great medicolegal expert, and a great Canadian.

He was a pioneer with that small group of Canadian pathologists upon whose shoulders fell the mantles of an Adami and of a Mackenzie. He was easily in the front rank of histopathologists on this continent and abroad. In difficult problems in cancer diagnosis his opinion was widely sought and seldom questioned. His presentations at meetings of pathologists and physicians were always of a high order and were accepted as authoritative. His research into the structure and functions of the spleen was a very material contribution to the knowledge of the subject.

His wide and deep knowledge of pathology, his orderly mental processes, his clarity of expression, and his love of teaching, were all reflected in lectures and demonstrations of surpassing quality. The impact of his great ability, and of the charm of his personality on succeeding generations of medical students for more than 30 years, was of incalculable value to Canadian Medicine. Thousands of Canadian physicians are, today, better men and better physicians because of him.

As a medicolegal expert he had few equals. His thorough knowledge of the subject, his ability to express clearly what he meant, and the logic of conclusions drawn, made him the ideal expert witness. His innate sense of fairness and justice, and his strict impartiality, earned him the respect of both prosecution and defense. He played a part in many of the more important criminal trials in Toronto and Ontario for well-nigh 30 years, and his opinions and conclusions were rarely contested. His great ability in this field was attested by the fact of his appointment as consultant in medicolegal matters to the Government of Ontario.

But those of us who were his classmates, and, particularly, those of us whose good fortune it was to be more closely associated with him in professional or other capacities during his busy life of service at the Banting Institute, acknowledge a special debt of gratitude. He always had time for his friends. No trouble was too great when a colleague needed and sought advice and assistance. His loyalty to his ideals, his philosophy of life and of living, his understanding and love of human nature enthroned him in the hearts of all who came to know him well.

He has passed to his reward, leaving with us a rich legacy of service and achievement, and a memory which will not soon fade. In the words of the immortal John McCrae, author of "Flanders Fields,"

> "God meteth him not less, but rather more,
> Because he sowed, and others reaped his store."

DR. WILLARD P. THOMPSON, 55, died in Chicago, Ill., on March 23. Born in Fredericton, N.B., he graduated from Harvard University medical school and became one of the leading endocrinologists in the United States. He was a clinical professor of medicine at the University of Illinois College of Medicine. Dr. Thompson served as president of the American Geriatric Society and was a former president of the American Goiter Association and the Chicago Medical Society.

DR. JOHN WEBSTER, a pioneer in Canadian neurosurgery, died at Whitby, Ont., on March 26. Born in Toronto, he graduated from the old Toronto Medical School in 1889 and in the following year he entered the Ontario Mental Hospital Service where he remained for 48 years. He was at the Kingston Hospital from 1890 until 1900 and for the next 20 years was at Hamilton. In 1920 he joined the staff of the Ontario Hospital at Whitby where he became assistant superintendent. In 1934 he retired officially but continued as radiologist for another four years. Dr. Webster was believed to be the first surgeon in Ontario to operate in search of brain scar tissue. He published a paper on this subject in 1894. He was widely known for his contributions to his chosen branch of medicine and, up until a month before he died, he watched with interest the latest developments in the field of mental health and the expansion of the Ontario Mental Hospital Service. Dr. Webster passed his 90th birthday the week before his death. He is survived by one daughter.

ABSTRACTS *from current literature*

MEDICINE

An Evaluation of Anticoagulant Therapy in Myocardial Infarction Based on Prognostic Categories.

FURMAN, R. H., BALL, C. O, T., GALE, R. G., BILLINGS, F. T. JR. AND MENEELY, G. R.: AM. J. MED., 14: 681, 1953.

Dicoumarol or dicoumarol and heparin were administered during 100 episodes of acute myocardial infarction. An earlier group of 211 patients served as controls. Patients were sorted into prognostic categories according to the following criteria: (1) Very poor risks: (a) the attack was the patient's first; shock and diabetes or shock and azotæmia were present; (b) a previous attack had occurred; shock was present or congestive failure and diabetes and azotæmia were present. (2) Poor risks: shock, congestive failure, diabetes or azotæmia was present within the first week of admission. (3) Good risks: none of the concomitant manifestations in groups 1 and 2 were present.

Anticoagulants failed to improve the mortality in the "very poor risk" category. The mortality in the "good risk" category was very small with or without anticoagulants. The beneficial effects of anticoagulants were most apparent in the "poor risk" group of patients and then chiefly so in those less severely ill. Such beneficial effects cannot be entirely ascribed to a reduction in incidence of thromboembolic phenomena.

The need for further evaluation of anticoagulant therapy in myocardial infarction within a framework of prognostic categories is emphasized. S. J. SHANE

Parenteral Administration of Trypsin: Clinical Effect in 538 Patients.

INNERFIELD, I., ANGRIST, A. AND SCHWARTZ, A.: J. A. M. A., 152: 597, 1953.

This paper presents clinical observations on 6,456 trypsin infusions in 538 patients, which suggest that trypsin

rapidly suppresses acute inflammation of diversified origin (bacterial, viral, allergic, and chemical). For each treatment, a vial containing 10 mgm. of trypsin was dissolved in 3 c.c. of isotonic sodium chloride. This solution was then added to 100 c.c. of isotonic sodium chloride, and 1 c.c. (10 mgm.) of methapyrilene hydrochloride (Histadyl) was introduced into the flask. The intravenous infusion was started immediately following preparation of the solution, and each dose consisted of 10 to 15 mgm. of trypsin dissolved in 100 c.c. of isotonic sodium chloride solution. A typical course of therapy consisted of 10 mgm. of trypsin per infusion, twice daily for 5 to 7 consecutive days. Types of cases treated included acute rheumatoid arthritis, acute thrombophlebitis, primary atypical pneumonia, diabetic carbuncle, acute meningoencephalitis, acute sinusitis, acute ulcerative colitis, and many others. Prompt subsidence of the signs of acute inflammation is reported to have occurred in almost all cases. No significant untoward side-effects were noted. It appears that, in a manner as yet unexplained, trypsin activates a system of naturally occurring enzymes, which participate in determining the rate at which inflammatory processes subside, thereby enabling healing to follow. In other words, trypsin appears to catalyse enzymatic sequences that augment the host reaction to injury. S. J. SHANE

The Hæmatological and Nutritional Effects of Gastric Operations.

BLAKE, J. AND RECHNITZER, P. A.: QUART. J. MED., 22: 419, 1953.

This study comprises a careful investigation of the effects of gastric surgery on the blood picture and general nutrition of a group of 179 patients (partial gastrectomy 104, gastroenterostomy 65, and total gastrectomy 10 cases). Iron-deficiency anæmia occurred in 40% of the males and 45% of the females following partial gastrectomy, and in 20% after total gastrectomy (all 10 patients in this series with total gastrectomy were males); no evidence of iron-deficiency anæmia was found after gastroenterostomy. Macrocytic anæmia was present in one woman after partial gastrectomy and in six of the 10 males after total gastrectomy.

Malnutrition, as evidenced by vitamin-B deficiency, was present in 4% of men and 5% of women after partial gastrectomy, and in three out of 10 after total gastrectomy; it was not found after gastroenterostomy. Significant weight loss followed partial gastrectomy in 4% of men and 23% of women, whereas after gastroenterostomy it occurred in only 2% of males and 8% of females. Weight loss was significant in five of the 10 total gastrectomy patients. NORMAN S. SKINNER

Cholecystography in the Presence of Liver Disease.

ETESS, A. D. AND STRAUS, B.: NEW ENGLAND J. MED., 249: 930, 1953.

The present study was made to assess the value of oral cholecystography in the presence of liver disease but in the absence of jaundice. Iodoalphionic acid (Priodax) was administered to 35 such patients, none of whom had history or symptoms suggestive of primary gall-bladder or biliary-tract disease. If the gall-bladder was not visualized after the first dose of 6 gm. the procedure was repeated on the next day. The gall-bladder was visualized normally in all of 23 patients whose bromsulphalein retention was less than 20%, faintly in five cases with retention between 20 and 23% and not at all in seven patients with a bromsulphalein retention greater than 23%.

The authors conclude that oral cholecystography is diagnostically reliable in the presence of chronic liver disease without jaundice if the bromsulphalein retention is less than 20%. No toxic effect was evident following the administration of Priodax to these patients.

NORMAN S. SKINNER

Bed Rest in the Treatment of Pulmonary Tuberculosis.

DEFRIEZ, A. I., PATTON, W. E., WELCH, E. J. AND BADGER, T. L.: NEW ENGLAND J. MED., 250: 39, 1954.

The importance of complete bed rest in the treatment of tuberculosis should be assessed as accurately as possible, to serve as a baseline for comparison with the results of modern chemotherapeutic and surgical attacks upon the disease. To acquire such a baseline the authors studied the records of 377 consecutive patients with pulmonary tuberculosis admitted to the Channing Home between 1930 and 1944. The minimal period of follow-up was five years. The various forms of collapse therapy were employed in these patients. The relapse rate was found to be 39% for minimal and 56% for advanced forms of the disease. Patients subjected to thoracoplasty showed a 33% relapse rate. Seventy per cent of all relapses occurred within five years of discharge.

NORMAN S. SKINNER

SURGERY

Surgical Treatment of Arteriosclerotic Aneurisms of the Abdominal Aorta.

KIRKLIN, J. W., WAUGH, J. M., GRINDLAY, J. H., OPENSHAW, C. R. AND ALLEN, E. V.: ARCH. SURG., 67: 632, 1953.

Three methods of surgical attack on abdominal aneurisms have been used at the Mayo Clinic. Thromboendarterectomy was performed through a transabdominal approach, the aneurism dissected free and the inferior mesenteric artery and some lumbar arteries and veins divided. Through a long incision in the aorta, thrombus and calcified intima were removed and the aneurism was trimmed down and closed to form a normal-sized tube. Heparin was used and the aorta reinforced with a wrapping of fascia lata and polyvinyl sponge. Recently a bilateral sympathectomy has been added to the operation. Resection and replacement by aortic graft was done by using a preserved homologous graft to take the place of the aneurism. This was also accompanied by bilateral lumbar sympathectomy. Reinforcement with polyvinyl sponge was the most frequent procedure.

The polyvinyl sponge and thromboendarterectomy methods have proved disappointing. The one patient who had a homologous graft replacement had an excellent immediate result. Reinforcement with polyvinyl sponge gave relief from pain in a number of patients.

Longer follow-up of more patients is necessary before final evaluation of these methods can be made, but the homologous graft technique seems promising in certain cases. BURNS PLEWES

Fat Embolism.

ALLDRED, A. J.: BRIT. J. SURG., 41: 82, 1953.

Fat embolism probably occurs much more frequently than is recognized; though known as a clinical entity for a long time, it is poorly understood. Symptoms usually begin 36 or 48 hours after a fracture, the first change being restlessness with fever, often pain in the chest and slight dyspnœa. The patient shows cyanosis and uneasiness, with a rising pulse and normal blood pressure. Cerebral signs, ranging from irrational changes to coma, develop. Incontinence of urine is a striking sign in a patient who has previously shown no such tendency. A petechial rash is most frequent over the upper chest, neck, shoulders and often the conjunctiva. Moist sounds are heard over the chest. In the nine cases described none had fundus changes, two showed a snowstorm effect in chest radiographs and two had fat in the urine. Three out of the nine patients died, all within 24 hours. The prognosis is determined early and can be given in

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the first hour: most serious is the rapid development of deep coma, for it indicates a great amount of fat in the circulation. Cases without coma have a good prognosis, and recovery from brain involvement is good though perhaps slow.

The source of the fat in fat embolism is almost always the long bones of the lower limbs. Entering the venous circulation, the fat travels via the right heart to the lungs, producing the symptoms of pulmonary embolism. Passing through the lung capillaries, the fat is carried to the best arterialized parts of the body—brain, kidneys and heart. Perhaps the location of the skin petechiæ is due to the physical properties of the fat and the forward, direction of the thyroid axis artery, vertical when the patient is supine. BURNS PLEWES

Acute Abdominal Emergencies in Infancy and Early Childhood.

GILLESPIE, C. E. AND MOORE, C. H.: ARCH. SURG., 66: 741, 1953.

Acute surgical emergencies in children under 5 years of age are not common, only 158 cases being found in 188,375 admissions to the John Gaston Hospital in Memphis. There were 16 cases of appendicitis and no patient died—an extraordinary record. Of 42 patients with intussusception, 36 were between 3 and 11 months old, and five died. Two died after resection of gangrenous bowel, and three cases were diagnosed at autopsy. Hypertrophic pyloric stenosis occurred 23 times; 22 patients were males. Two died after a Ramstedt pyloromyotomy. There were 47 patients with irreducible hernias (44 inguinal and 3 umbilical), and one postoperative death. Incarcerated hernias are regarded as extreme emergencies and attempts at reduction are frowned upon. There were 4 cases of intestinal obstruction due to adhesions, 3 cases of malrotation of the colon, one case of traumatic diaphragmatic hernia, and one of annular pancreas. In 10 cases of omphalocele, there was a mortality rate of 40%. Three out of eight patients with imperforate anus died, all having multiple anomalies. All three cases of atresia of the bile ducts were operated upon; in the one in which an anastomosis was possible the child survived. No cases of Meckel's diverticulitis, retroperitoneal tumour, ruptured spleen or meconium ileus occurred in this 10 year period.

BURNS PLEWES

Use of Dextran in Control of Shock Resulting from War Wounds.

AMSPACHER, W. H. AND CURRERI, A. R.: ARCH. SURG., 66: 730, 1953.

In spite of a natural reluctance on the part of medical officers to employ a plasma expander with which they were not familiar, the same doctors became enthusiastic after they had observed the response of wounded patients to dextran. Though most of the casualties were in shock, partially at least because of blood loss, the recovery when dextran was used was prompt and blood was given only when the hæmatocrit level decreased to 20% or less. The patients were United Nations soldiers and prisoners brought to a Mobile Army Surgical Hospital in Korea. There were no reactions, either immediate or delayed, in the 60 cases reported, nor were there renal complications. Three of the casualties died, but autopsies failed to reveal any evidence to incriminate dextran.

There is no true substitute for whole blood and the latter should be conserved. Conservation can be accomplished by using it only when the wound and blood loss are severe and augmenting it with a suitable plasma expander. BURNS PLEWES

OBSTETRICS AND GYNÆCOLOGY

Rh Iso–Immunization.

GAINEY, H. L., NICOLAY, K. S., KEELER, J. E. AND DOYLE, M. E.: AM. J. OBST. AND GYNEC., 3: 141, 1954.

A group of Rh-negative immunized patients were studied to determine whether any common factors could be found to suggest the manner in which the patient became immunized. The history of 56% of these patients presented factors suggesting induced pathology. A group of non-immunized Rh-negative multiparas with Rh-positive husbands were studied. In only 7% of these patients did the history demonstrate the factors which were incriminated in the study group.

A plea is made for reducing the opportunities for these patients to become sensitized as a result of preventable pathology or for enhancing the uncontrolled natural avenues of antigen stimulation. Pregnant Rh-negative women should be treated with the greatest respect and given the utmost in non-traumatic and conservative care.

ROSS MITCHELL

Transabdominal Encephalocentesis in a Case of Congenital Hydrocephalus.

FARA, F. J., FOSS, H. G. AND PHILIPP, E. A.: AM. J. OBST. AND GYNEC., 67: 138, 1954.

A case report illustrating a technique for the management of breech presentation with a hydrocephalic infant is discussed. If fluid is drawn off the restoration of uterine tone is likely to initiate labour and shorten the first and second stages, as well as minimize the most common maternal complications of hydrocephalus, i.e., rupture of the uterus, post-partum hæmorrhage and post-partum morbidity.

Technically the procedure was easier and much less traumatizing than many cases of craniotomy on the aftercoming head. ROSS MITCHELL

Physiological Salpingitis.

NASSBERG, S., MCKAY, D. G. AND HERTIG, A. T.: AM. J. OBST. AND GYNEC., 67: 130, 1954.

A non-bacterial acute salpingitis occurring at the time of menstruation was found in 62% of patients who were menstruating. The inflammatory reaction was characterized by a polymorphonuclear leukocyte infiltration, œdema of the stroma of the plicæ, dilatation of lymphatic vessels of the plicæ, leukostasis, and menstrual blood in the tubal lumen.

The possible origin and significance of this inflammatory reaction are discussed. ROSS MITCHELL

Some Lessons from 4,000 Utero-Tubal Insufflations.

SHARMAN, A.: BRIT. M. J., 1: 239, 1954.

Some of the more important lessons gained from just over 4,000 tubal insufflations during the past 25 years are: (1) Practice bears out the theoretical advantages of carbon dioxide. There were only five cases of infection and no deaths. (2) Two or more tests, with the pressure advanced to 250 mm. Hg., one at least without anæsthesia, provide a reliable diagnosis of non-patency. (3) Primarily sterile women numbering 902 were followed up for 12 months; 30% became pregnant. In a group of 253 patients in whom a uterine sound was passed, only 18% became pregnant within twelve months. (4) The kymograph is a useful adjunct.

ROSS MITCHELL

PÆDIATRICS

Resuscitation of the Newborn with Intragastric Oxygen. (Akerren's Method).

WALLER, H. K. AND MORRIS, D.: LANCET, 2: 951, 1953.

The primary cause of depression of the respiratory centres of the asphyxiated newborn may be unknown, but it is certain that lack of oxygen in the blood stream furthers that depression, which may lead to a fatal secondary anoxia. Time being of the essence in getting oxygen to the brain, the authors point out a safe method here. Its value is increased tenfold in that it is gentle, and can be safely used either in the home or hospital. Akerren first reported his use of intragastric oxygen on the asphyxiated full-term infant in 1950. The authors used the method for 48 infants, 41 of whom were saved.

Intragastric oxygen is quickly absorbed by the capillaries of the stomach and the equipment used to provide it consists of the following: (1) Two pairs of sterilized Jacques catheters, sizes 3 and 5. One of each pair serves as the inlet and has a glass connection for attachment to the pressure tubing of an oxygen cylinder. The second of each pair serves as a safety or outlet catheter. (2) Oxygen cylinders—for home delivery the small, portable size can be used. (3) In home delivery rubber tubing and a pressure bag should also be at hand. (4) A small glass vessel or gallipot.

The method employed is as follows: (1) The size of tube to suit the infant is chosen and the safety tube is passed. The contents of the stomach are aspirated and then the tube is placed under water in the vessel or gallipot. (2) The inlet tube attached to the cylinder of oxygen is also passed and oxygen at the rate of one litre per minute is introduced. In a few moments the stream of bubbles in the vessel will show that oxygen is safely leaving the stomach. (3) The apparatus is left in place until the infant is breathing spontaneously. The distended outline of the infant's stomach will be immediately visible. Sometimes the intestines will bulge, but with the apparatus working as described a flow of one litre per minute is safe.

Equipment assembled for home use weighs about 5 pounds. The hospital nurse is quite competent to use this method.

ISABEL M. LAUDER

Combined Immunization.

LAPIN, J. AND WEICHSEL, M.: POST-GRAD. M. J., 14: 425, 1953.

There is an astounding decline in the percentage of Schick-negative pregnant women, indicating a lack of subclinical immunization and hence a lack of transplacental transference of diphtheria antitoxin to the infant. This leads the authors to reassess the field of infant immunization.

After a thorough résumé of the different types of antigens and their combinations, the decision is reached that diphtheria, tetanus, and pertussis prophylactics can safely be given the infant in a triple combination, beginning at three months and carried through the ninth month, as the Alhydrox triple mixture. Although there is a certain antigenic inefficiency in the very young infant, a booster dose six months after the initial course will compensate for this. The initial course is carried through in three or four injections of 0.5 c.c. each, at monthly intervals. In order to avoid reactions, it is best to start with a mixture containing 10 billion *H. pertussis*, and increase to 20, 30, and 40 billion. Booster doses should be given (0.5 c.c.) at 12 or 18 months, at 2½ or 3½ years, and before the child enters school. Since subclinical infections with diphtheria are becoming rarer, booster doses at two year intervals will have to be continued almost into adult life. This regimen is thought to be rigorous enough to rule out *gravis* infection.

Reactions are mild in young infants, but they cannot be disregarded in older children and adults. It is important to remember that large booster doses will produce severe reactions, and the Maloney test for sensitivity should be used before injection. Pertussis vaccine causes redness, swelling, induration, regional adenitis, and occasionally ecchymotic areas. Pain and subfebrile temperatures will be noticed in 10 to 40% of children. There have been no new reports of encephalopathy since 1949, and it seems possible that new methods of preparation, and the new National Institute of Health requirements for ageing of the vaccine have diminished the possibility of this dangerous reaction. However, no child who has a history of convulsions, or who is ill in any way, should have the injections as normally recommended.

The relationship of poliomyelitis to recent immunization procedures has not been established. It is thought that dirty equipment might play a part in the possible relationship.

ISABEL M. LAUDER

Children in Hospital: Preparation for Operation.

MACKEITH, R.: LANCET, 2: 843, 1953.

The younger the child the more he is bound to suffer anxiety and feelings of rejection when he is taken to hospital for treatment and surgery. The author classes as three main anxieties, separation from home, anæsthesia, and the operation.

Many children, if over five, seem quickly to forget the hospital experience, and a few seem to behave better since they have survived an experience they thought would be bad—they actually have more self-confidence. Smaller children may exhibit regressive behaviour for a time, such as bedwetting and fear of being alone by day or night. Increased dependency on the mother is the commonest sequel at all ages.

The doctor and the parents must work together over the child's hospital stay. The following suggestions should be helpful: (1) Give the child a forthright and honest explanation of the reasons for surgery. (2) Explain something of the hospital set-up in advance. Don't take a child into his experience without some idea of what it will be: describe nurses and doctors to him. (3) Reassure the child that the anæsthetic is something to shield him from pain and that he will awaken safely. Let the child carry a well-loved toy or article from home with him. It is less frightening to the child if he is allowed to walk to the surgical area rather than carried down on a stretcher. If the doctor can lead the child to the area himself, it is thought that the child-doctor rapport will be strengthened. (4) Permit expression of hostile feelings on the child's part immediately after operation. This is much better than suppression. Emphasize to the parents the need for constant reassurance and affection in the postoperative period.

Probably most important of all is the advice of many pædiatricians and child psychologists to postpone operations if at all possible until the child is four. It is least disturbing at this age to separate him from his mother. Also, if there has been another recent separation, such as a previous stay in hospital, a family bereavement, the advent of another baby, or a family move into a new home, it is best to postpone operation. If this cannot be done, then special care and attention must be given.

ISABEL M. LAUDER

Investigating Narcotic Addiction in School Children.

JACOBZINER, H.: AM. J. PUB. HEALTH, 43: 1138, 1953.

The outbreak of drug addiction in the New York City schools during 1950-51, continuing into the first months of the 1951-52 school year, proved to be a public health problem which yielded to standard epidemiological techniques. This, a new type of epidemic, was studied carefully by the school health service with the aid of the

teaching personnel and police. Mistakes were made at the beginning but soon corrected.

The main difference in this epidemic was that drug addiction *per se* is not a primary disease entity but is symptomatic of a basic personality maladjustment. The author reports here on the background of 165 verified users (about 25% of the estimated number of addictions). It was found that: (1) the rate was highest in the vocational schools where a large number of underprivileged students are enrolled. Many were the product of broken homes. Of the total, 54% came from three schools located in critical areas. One school alone was responsible for 25% of the users. (2) Surprisingly enough, 89% were males. Press reports had magnified the number of girls involved. (3) The age group in which addiction was highest was the 15-17 year group. (4) Only 8 of the users had police records. (5) The only physical signs were numerous needle scars, punctures, and sclerosis of veins. (6) The majority started by smoking marijuana. They explained that the sensation was one of feeling "normal". Tensions and frustrations faded away. All knew where and how to obtain the drug.

The author concludes that the basic problems must be searched for in order to eradicate this evil practice. Legislation dealing with slum clearance and promotion of good housing is important. Narcotic addiction should be included in the reportable diseases. Also, a continued program of health education is necessary, and all possible sociological aid should be given to the underprivileged adolescent. Research must be continued. In short, this problem calls for an all-out community effort. New York's success in stemming the epidemic proves that it can be done. ISABEL M. LAUDER

THERAPEUTICS

Norepinephrine in Shock Following Myocardial Infarction—Influence upon Survival Rate and Renal Function.

SAMPSON J. J. AND ZIPSER, A.: CIRCULATION, 9: 38, 1954.

Severe and sustained hypotension complicating myocardial infarction is correlated with a fatality rate of 80 to 90%. It is thought that hypotension and the accompanying inadequate coronary circulation are detrimental to the functional integrity of the myocardium and therefore warrant prompt correction.

Prolonged intravenous norepinephrine (noradrenaline) therapy was given to 30 patients, from 43 to 84 years of age, in an attempt to influence immediate and eventual survival from shock. All had clinical and electrocardiographic evidence of recent myocardial infarction. The average dose of norepinephrine required to elevate and sustain the blood pressure was 7.5 micrograms per minute, although an optimal response in different patients was obtained with doses varying from 1.5 to 25 mcgm. per minute. If 25 mcgm. per minute proves of no avail, patients rarely respond to higher doses, although in isolated instances doses as high as 150 mcgm. per minute were found necessary. Large doses should always be tried before concluding that a patient is refractory to this treatment.

Twenty (67%) of the 30 patients survived the episode of shock under norepinephrine therapy, and 16 (53%) recovered clinically and were later discharged from hospital. Four patients died subsequently of other causes after shock had been treated successfully. Ten patients (33%) died during norepinephrine therapy. Although oliguria is a common complication of myocardial infarction, patients under norepinephrine therapy showed striking improvement in urine output, presumably due to elevation of effective filtration pressure. Congestive heart failure was not observed to increase in any of the cases during therapy. Two instances of arrhythmia were recorded. Six patients developed mild phlebitis above the site of venous infusion. One patient had a large slough where the solution leaked from a polyethylene tube in a vein of the lower leg.

The high percentage of recovery with continuous administration of norepinephrine is thought to be due to the artificial maintenance of blood pressure, which permits the organism to survive the critical period until the natural mechanisms for maintaining blood pressure are resumed. B. L. FRANK

Clinical Evaluation of Combined Hydrogenated Ergot Alkaloids (Hydergine) in Arterial Hypertension—With Special Reference to Their Action in Central Manifestations.

TANDOWSKY, R. M.: CIRCULATION, 9: 48, 1954.

One hundred patients suffering from sustained arterial hypertension, 44 women and 65 men with an average age of 51 and 56 years respectively, were studied over a period of two years during which parenterally administered hydrogenated ergot alkaloids were the main drug therapy. These alkaloids in a dosage of 0.3 mgm. produced a transient reduction in systolic and diastolic blood pressure and in pulse rate, which seldom exceeded two hours. The average reduction in systolic and diastolic pressure was 36 and 12 mm., and the pulse rate was reduced six beats per minute.

Hydrogenated ergot alkaloids were found to be of value in the presence of early cerebral complications associated with arterial hypertension; in some instances, they may have averted serious cerebral accidents. Because of their rapid elimination when given parenterally, these alkaloids in the dosage recommended appear to be harmless and the author advises their use in the treatment of hypertensive patients. B. L. FRANK

FORTHCOMING MEETINGS

CANADA

CANADIAN SOCIETY OF PLASTIC SURGEONS, Seigniory Club, Que. (Secretary, Dr. J. V. R. Ord, 170 St. George Street, Toronto, Ont.) June 4-6, 1954.

CANADIAN NURSES' ASSOCIATION, 27th Biennial Meeting, Banff Springs Hotel. (Canadian Nurses' Association, National Office, Room 401, 1411 Crescent Street, Montreal, Que.) June 7-11, 1954.

INTERNATIONAL CONGRESS OF PSYCHOLOGY, Montreal, Que. (Prof. H. S. Langfeld, International Union of Scientific Psychology, Eno Hall, Princeton University, Princeton, N.J.) June 7-12, 1954.

SSCIETY OF OBSTETRICIANS AND GYNÆCOLOGISTS OF CANADA, Annual Meeting, Harrison Hot Springs, B.C. (Dr. R. B. Meiklejohn, Secretary, Toronto Western Hospital, Toronto, Ont.) June 10-13, 1954.

CANADIAN MEDICAL ASSOCIATION, Annual Meeting, Vancouver, B.C. (Dr. T. C. Routley, General-Secretary, 244 St. George Street, Toronto 5, Ont.) June 14-18, 1954.

CANADIAN TUBERCULOSIS ASSOCIATION, Saint John, N.B. (Dr. G. J. Wherrett, Executive Secretary, Canadian Tuberculosis Association, 265 Elgin Street, Ottawa 4, Ont.) June 24-26, 1954.

INTERNATIONAL CONFERENCE ON GROUP PSYCHOTHERAPY, Toronto, Ont. (Dr. Wilfred C. Hulse, Chairman. International Committee on Group Psychotherapy, 110 West 96th Street, New York 25, N.Y.) August 12-19, 1954.

INTERNATIONAL CONGRESS ON CHILD PSYCHIATRY, University of Toronto, Toronto, Ont. (Miss Helen Speyer, Executive Officer, International Association for Child Psychiatry, 1790 Broadway, New York 19, N.Y) August 13-14, 1954.

INTERNATIONAL CONGRESS ON MENTAL HEALTH, University of Toronto, Toronto, Ont. (The Executive Officer, Fifth International Congress on Mental Health, 111 St. George Street, Toronto, Ont.) August 14-21, 1954.

INTERNATIONAL CONGRESS OF OPHTHALMOLOGY, Montreal, Que. (Dr. G. Stuart Ramsey, Associate Secretary, Physical Sciences Centre, McGill University, Montreal 2, Que.) September 9-11, 1954.

INDUSTRIAL MEDICAL ASSOCIATION OF THE PROVINCE OF QUEBEC, AND THE INDUSTRIAL SECTION OF THE ONTARIO MEDICAL ASSOCIATION, Joint Meeting, Ottawa, Ont. (Dr. W. F. Prendergast, Secretary of the Section of Industrial Medicine, 22 Commercial Road, Leaside, Toronto 17, Ont.) September 23-25, 1954.

UNITED STATES

NATIONAL CONVENTION OF THE AMERICAN SOCIETY OF MEDICAL TECHNOLOGISTS, Annual Convention, Miami Beach, Florida. (Mrs. Maxine T. Ace and Mrs. Anna L. Rundell, Co-chairman, Publicity Committee, Jackson Memorial Hospital, Miami, Florida) June 13-17, 1954.

MEDICAL LIBRARY ASSOCIATION, Annual Meeting, Washington, D.C. (Lt. Col. Frank B. Rogers, Armed Forces Medical Library, 7th Street and Independence Avenue, S.W., Washington 25, D.C.) June 15-18, 1954.

AMERICAN GERIATRICS SOCIETY, Annual Meeting, San Francisco, Calif. (Dr. W. O. Thompson, President, 700 North Michigan Ave., Chicago 11, Ill.) June 17-19, 1954.

AMERICAN COLLEGE OF CHEST PHYSICIANS, Annual Meeting, San Francisco, Calif. (Dr. Edgar Mayer, Chairman of the Committee on Scientific Program, 850 Fifth Avenue, New York 21, N.Y.) June 17-20, 1954.

AMERICAN MEDICAL ASSOCIATION, Annual Meeting, San Francisco, Calif. (Dr. George F. Lull, 535 North Dearborn Street, Chicago 10, Ill.) June 21-25, 1954.

ANNUAL SYMPOSIUM ON TUBERCULOSIS AND OTHER CHRONIC PULMONARY DISEASES FOR GENERAL PRACTITIONERS, Saranac Lake, N.Y. (Dr. Richard P. Bellaire, P.O. Box 2, Saranac Lake, N.Y.) July 12-16, 1954.

INTERNATIONAL COLLEGE OF SURGEONS, Convention of the Canadian and American Sections, Chicago, Ill. (Dr. E. N. C. McAmmond, Secretary, Canadian Section, Suite 2, 1701 Broadway West, Vancouver 9, B.C.) September 7-10, 1954.

INTERNATIONAL CONGRESS OF OPHTHALMOLOGY, New York, N.Y. (Dr. William L. Benedict, Secretary-General, 100 First Avenue Building, Rochester, Minn.) September 12-17, 1954.

WORLD CONGRESS OF CARDIOLOGY, Washington, D.C. (Dr. L. W. Gorham, Secretary-General, Second World Congress of Cardiology, 44 East 23rd Street, New York 10, N.Y.) September 12-17, 1954.

INTERNATIONAL ANÆSTHESIA RESEARCH SOCIETY, Annual Congress, Los Angeles, Calif. (Dr. T. H. Seldon, Chairman, 102-110 Second Avenue, S.W., Rochester, Minn.) October 4-7, 1954.

OTHER COUNTRIES

IRISH MEDICAL ASSOCIATION, Annual Meeting, Killarney, Ireland. (Dr. P. J. Delaney, Medical Secretary, 10, Fitzwilliam Place, Dublin) July 7-10, 1954.

INTERNATIONAL GERONTOLOGICAL CONGRESS, London and Oxford, England. (Prof. R. E. Tunbridge, President, Department of Medicine, The University, Leeds, England) July 12-22, 1954.

INTERNATIONAL CONGRESS ON THROMBOSIS AND EMBOLISM, Basle, Switzerland. (Dr. W. Merz, Hon. Secretary, Gynæcological Clinic, University of Basle, Switzerland) July 15-19, 1954.

INTERNATIONAL CONGRESS FOR PSYCHOTHERAPY, Zürich, Switzerland. (Dr. H. K. Fierz, Secretary General, Theaterstrasse 12, Zürich 1, Switzerland) July 21-24, 1954.

INTERNATIONAL CANCER CONGRESS, Sao Paulo, Brazil. (Prof. A. Prudente, 171 rua Benjamin Constante, Sao Paulo, Brazil) July 23-29, 1954.

INTERNATIONAL CONGRESS ON OBSTETRICS AND GYNÆCOLOGY, Geneva, Switzerland. (Dr. H. de Watteville, President, Maternité, Hôpital Cantonal, Geneva, Switzerland) July 26-31, 1954.

THIRD INTERNATIONAL POLIOMYELITIS CONFERENCE, Rome, Italy. (Secretariat: 6 via Lucullo, Rome, Italy. Cable address: Inpolio, Rome.) September 6-10, 1954.

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Stockholm, Sweden. (Secretariat of the Third International Congress of International Medicine, Karolinska sjukhuset, Stockholm 60, Sweden) September 15-18, 1954.

CONFERENCE OF THE INTERNATIONAL UNION AGAINST TUBERCULOSIS, Madrid, Spain. (Prof. Alix y Alix, Escuela di Tisiologia, Ciudad Universitaria, Madrid, Spain) September 26-October 2, 1954.

PAN-PACIFIC SURGICAL ASSOCIATION, Congress, Honolulu, Hawaii. (Dr. F. J. Pinkerton, Director General, Pan-Pacific Surgical Association, Young Building, Honolulu, Hawaii) October 7-8, 1954.

JAPAN MEDICAL CONGRESS, Kyoto, Japan. (Dr. M. Goto, Secretary General, University Hospital, Medical Faculty of Kyoto University, Kyoto, Japan) April 1-5, 1955.

INTERNATIONAL DIABETES FEDERATION, Cambridge, England. (Secretary, P. Duys, 33, Prinsegracht, The Hague.) July 4-8, 1955.

CONGRES DE LA LITHIASE URINAIRE, Evian, (Hte-Savoie), France. (Séc. Prof. Agr. Cl. Laroche, 16, rue Christophe-Colomb, Paris (8e), France) 2-4 septembre, 1955.

NEWS ITEMS

ALBERTA

The very peculiar April winter-like weather has been blamed on many things, and all records have been shattered. Sunny Alberta will have to make up for lost time this year. Many of the ardent medical fishermen are taking along little ice-cutting axes just in case.

The Annual Refresher Course, put on by the University of Alberta Faculty of Medicine, was conducted May 3 to 7 inclusive. Dr. C. C. Ferguson of the University of Manitoba; Dr. A. M. Agnew of the University of B.C. and Dr. M. M. Wintrobe of the University of Utah were the outside speakers.

The new poliomyelitis treatment wing of the University Hospital is under construction. It will extend west of the new wing.

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There were approximately 30 new Canadians up for their Dominion Council examinations this year in Alberta; this shows encouraging progress being made by these fine new adherents of our Canadian way of life. We wish them all continued success in the profession.

Dr. P. M. Campbell of Lethbridge is active in the practice of his Art, namely medicine. We wish him many more years added to his present excellent record. Dr. Campbell is also director of the Cancer Diagnostic Clinic in that City. W. CARLETON WHITESIDE

BRITISH COLUMBIA

The outstanding event of the year in British Columbia from a medical standpoint, was the graduation during May of the first class to enter the Medical Faculty of the University of British Columbia (Med. '54, U.B.C.). This took place on May 17 at a special Convocation at the University. The number of graduates was approximately 60.

The final examinations were set by the General Medical Council of Canada: the University having entered into an agreement with this body to set the final examinations for each graduating class, in which the students qualify for the degree of M.D.

The *Bulletin of the Vancouver Medical Association* is publishing a special number (May) in commemoration of this event.

The annual meeting of the Council of College of Physicians and Surgeons of British Columbia was held on April 10. Dr. Roy Huggard of Vancouver was elected President of Council, to succeed Dr. Roy Walker of Penticton; Dr. L. Chipperfield became Vice-president, succeeding Dr. Huggard, while Dr. R. G. Langston takes Dr. Chipperfield's place as Treasurer. Dr. Lynn Gunn continues as Registrar.

The annual meeting of the Vancouver Medical Association, held on May 4, elected the following to the main offices of the society: President—Dr. J. Howard Black; Vice-president—Dr. F. S. Hobbs; Treasurer—Dr. R. A. Gilchrist; Hon. Secretary—Dr. G. E. Langley; Trustee—G. H. Clement; Editor—Dr. J. H. MacDermot; Executive members—Dr. A. F. Hardyment and Dr. Paul Jackson.

A feature of the Convocation was the bestowal of honorary Doctor of Science degree on two outstanding medical people, Dr. Ethlyn Trapp of Vancouver, and Dr. Brock Chisholm, now residing in B.C.

Dr. Trapp (McGill '27) is well known throughout Canada as an exceedingly accomplished radiologist. She is the first woman to have been president of the B.C. Medical Association, and is a native daughter of B.C. All who know her agree that she fully deserves this honour.

Dr. Brock Chisholm is a world figure in medicine, and needs no introduction. He is a Toronto graduate ('24) and has been eminently successful as a psychiatrist, a soldier, and administrator; his last active job, indeed, was as director of the World Health Organization.

Medical Services Incorporated will shortly come into full operation in British Columbia, and organization is proceeding rapidly. More will be said about this later.

Campbell River, V.I., is going ahead with the organization of a new 60-bed hospital, which will cost taxpayers nearly a million dollars. The present Lourdes Hospital, operated by the Order of Ste. Anne, is becoming quite inadequate, and more hospital accommodation of the acute type has become an urgent necessity in this growing community.

The annual meeting of the Public Health Institute was held in April at the Hotel Georgia, Vancouver, and a large number of representatives of health units, public health nurses, etc., attended. The Institute lasted four days. J. H. MACDERMOT

NEW BRUNSWICK

Following a forum on "Prepaid Medical Care" at the 1953 annual meeting of the New Brunswick Medical Society it was decided that the executive committee set up a reference committee for Blue Shield to co-operate with the Blue Shield Division of the Maritime Hospital Association to control the use and application of the Blue Shield Plan in New Brunswick. This committee comprises: Dr. A. L. Donovan of Saint John as Chairman; Dr. J. A. M. Bell of Fredericton; and Dr. Paul Melanson of Moncton. It represents the doctors of New Brunswick and will seek to protect the interest of physicians, curtail abuses and provide wise counsel to those doctors who ask for or need such advice.

The southern section of New Brunswick was honoured by a visit from Dr. Wesley Bourne, who addressed the Fredericton Medical Society on the subject, "Factors Involved in the Choice and Administration of an Anæsthetic". This interesting subject was gilded by the addition of examples of Dr. Bourne's philosophy. Dr. Bourne continues to be agreeable as well as distinguished and kindly arranged to speak at an afternoon meeting so as to allow hockey enthusiasts to attend the semi-final playoffs in which the Fredericton team is engaged. Among Saint John physicians attending this lecture were: Dr. Fred Jennings; Dr. Ruth Brown; Dr. Edmund Lunney; and Dr. George Skinner.

Dr. E. F. Woolverton, President of the New Brunswick Medical Society accompanied by Dr. F. L. Whitehead, Secretary, visited the Moncton Medical Society on April 22 and discussed subjects of current interest in the C.M.A. projects as well as matters of local interest. The meeting was held in the Moncton Hospital.

The Saint John Medical Society Spring Clinical Session was held on April 6, 7 and 8 in the Pathological Institute. The Committee of Arrangements included: Dr. H. A. Bird, Chairman; Dr. A. L. Donovan; Dr. W. D. Miller; and Dr. F. L. Whitehead. Dr. Charles A. Janeway, Professor of Pædiatrics of Harvard University, presented addresses titled: (1) Clinical Manifestations of Hæmolytic Streptococcal Infections in Children. (2) Infection and Immunity in Infancy and Childhood. (3) Role of ACTH and Adrenal Steroids in Treatment of Disease in Childhood.

Dr. Norman F. Miller, Professor of Obstetrics and Gynæcology, University of Michigan discussed: (1) Handmaiden to Maternal Assassins. (2) When Hæmorrhage Strikes. (3) Common Lesions of the Cervix and What They Should Mean To Us.

Dr. Miller also met the Minister of Health of New Brunswick, Hon. Dr. J. F. McInerney and his deputies and the Clinical Advisory Committee of the N.B. Cancer Programme and discussed many angles of the diagnostic and therapy programme during which he referred broadly to the experience of similar plans in Michigan.

Panel discussions were provided by outstanding local physicians on the following subjects: (1) Anterior Chest Pain. (2) Investigation of the Gynæcological Patient. (3) Breech Presentations and Obstetrical Analgesia. (4) Urinary Tract Infections in Childhood. (5) Common E.N.T. Problems in Childhood.

The attendance at these meetings was excitingly large and the auditorium in the new Pathological Institute

proved an excellent setting for medical meetings. The acoustics in this roomy lecture hall are admirable. Our visiting friends from Ann Arbor, Michigan and Boston were so generous with their time and talents, wit and experience that the physicians of New Brunswick will be ever in their debt. It is still true that good medicine knows no geographical boundaries or other narrow confines.

Dr. Geo. M. White is recovering from a rather serious illness and is expected to be back on duty soon.

Dr. J. A. Melanson, Registrar-General of Vital Statistics for New Brunswick has begun the issue of a short form wallet size birth certificate for use in this province.

Dr. J. R. Mayers, Provincial Director of Maternal and Child Health reports several meetings with the N.B. Medical Society Committee on problems of his department and it has been proposed that each maternal death will be exhaustively studied on receipt of a new report form to be submitted in each such disaster. Meanwhile, efforts will be continued in education of physicians, nurses and the general public.

Dr. J. F. McInerney, Honourable Minister of Health of New Brunswick, attended Civil Defence Meetings at Ottawa and Arnprior. Dr. G. F. Bate of Rothesay is representing the Saint John General Hospital at a Regional Meeting of Civil Defence Organization at Halifax. Dr. C. O. McKay is representing Lancaster Hospital at the same meeting.

Dr. R. R. Prosser of Fredericton attended the executive meeting of the Canadian Psychiatric Association in February.

A. S. KIRKLAND

NOVA SCOTIA

The Hon. Harold Connely, Minister of Health for Nova Scotia, has been appointed premier of the province replacing the late Hon. Angus L. MacDonald.

"A Week in Surgery" was the title of a refresher course in surgery sponsored by the postgraduate committee of the Dalhousie Medical Faculty. Dr. J. C. Luke, Assistant Professor of Surgery, McGill University, Montreal and Dr. D. A. Thompson of Bathurst, N.B. were the guest speakers.

Dr. Luke gave three lectures on (1) Post-phlebitic Syndromes and Varicose Ulcers. (2) Diagnosis and Treatment of Occlusive Vascular Diseases. (3) Arterial Occlusion. Dr. Thompson's principal lecture was on "Trauma". In addition to the above guest speakers 35 members of the Dalhousie medical faculty took part in the five-day programme.

Those attending the course were Dr. G. Ritchie Douglas, New Glasgow; Dr. C. E. Doyle, Moncton; Dr. E. Dumont, Moncton, N.B.; Dr. J. S. Munroe, North Sydney, N.S.; Dr. J. H. MacLeod, Liverpool, N.S.; Dr. J. R. McLeave, Digby, N.S.; Dr. R. R. Strong, Grand Falls, Nfld.; Dr. A. L. Sutherland, Sydney, N.S.; Dr. R. G. A. Wood, Lunenburg, N.S.; Fl./Lt. W. A. Woodruff, Summerside, P.E.I. and Dr. J. A. F. Young, Pictou, N.S.

Dr. J. S. Robertson, Deputy Minister of Health for Nova Scotia is a member of a five man delegation to the annual meeting of the World Health Organization opening at Geneva, May 4.

Dr. Robertson sailed from New York on the liner *United States* April 30. Following the completion of the assembly meeting on May 21 he will spend a week in the United Kingdom visiting a number of medical centres.

Dr. Harold Read and Dr. William Murray, members of the Dalhousie Medical Faculty, were elected as associates of the American College of Physicians while attending the 35th annual meeting at Hotel Conrad Hilton, April 5 to 9.

Among the Nova Scotians who attended the spring sessional meeting of the American College of Surgeons in Montreal were Drs. Alan Curry, Arnold Noble, J. H. Charman, Leslie Stewart and M. D. Brennan.

C. M. HARLOW

ONTARIO

Dr. R. G. Bell, formerly medical director of Shadow Brook Health Foundation, has announced the opening of the Bell Clinic for the treatment of alcoholism at Willowdale, just north of Toronto. The hospital has private and semi-private accommodation. In addition there will be private accommodation in specially chosen homes in the vicinity under supervision of the Clinic nursing staff. Treatment will also be given on an outpatient basis. This includes group therapy and instruction programmes, psychological tests and follow-up.

Dr. R. G. Warminton, Niagara Falls, was named a Fellow of the Industrial Medical Association for his outstanding work in the field of industrial medicine. He received the Fellowship certificate at the annual meeting in Chicago.

A five year research project for the study of cancer in children has been developed by the Research Institute of the Hospital for Sick Children and the Ontario Cancer Research and Treatment Foundation. Dr. John Darte, who did research on leukæmia under the sponsorship of the National Cancer Research Institute and who studied in England as an exchange fellow under the British Empire Cancer Campaign will be in charge of this project.

Dr. N. A. McCormick, Windsor, was elected first vice-president of the American Radium Society at the annual meeting held at Warm Sulphur Springs, Virginia.

The annual meeting of the Canadian Mental Health Association was held in Toronto. Among the speakers were Dr. J. D. Griffin, national director of the Association, Dr. C. A. Roberts, chief of the Mental Division, Federal Department of Health and Dr. Jonathan Meakins, Montreal. Dr. Clarence Hincks, a pioneer in the mental health field, was presented with his portrait by the board of the Association.

Dr. Erich Baer has been awarded the Glycerine Research Award for 1953. The award consists of an honour plaque and $1,000. Dr. Baer received the honour for the synthesis of a group of glycerol derivatives present in animal cells, that is, in liver and brain tissue, which are extremely difficult to isolate from natural sources.

Although the principal value of Dr. Baer's discoveries is in pure research in the field of metabolism, they have already found practical applications. Individual synthetic glycerolphosphatides are being employed as substitutes for natural materials where the use of pure phosphatides is advantageous. Thus, synthetic L-alpha-lecithin, a stable compound of constant composition and serological activity, is rapidly replacing the beef-heart lecithin as antigen component in the serodiagnosis of syphilis.

Dr. Baer received his Ph.D. degree in chemistry from the Friederich Wilhelm University, Berlin. After appointments at the University of Berlin and the University of Basel, Switzerland, he became assistant research professor in the Department of Chemistry at University of Toronto in 1937. After joining the Banting

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and Best Department of Medical Research he was promoted to professor in 1951. For the past five years he has held the position of Head of the sub-department of synthetic chemistry in relation to medical research.

Dr. K. E. Hollis, formerly medical superintendent of Sunnybrook Hospital, has been appointed field officer under the Canadian Joint Hospital Commission. On this Commission there are representatives of the Royal College, the Canadian Medical Association, the Canadian Hospital Association and the Catholic Hospital Federation.

Genuine efforts are being made to improve hospital standards. Dr. Hollis, with his variety of experience, will bring to his work of hospital inspection a constructive attitude which will be of great help to governing bodies.

Toronto winners of travelling and research fellowships granted by the R. Samuel McLaughlin Foundation are Dr. John M. Finlay, Dr. Robert H. Sheppard, Dr. David J. Lewis, Dr. R. O. Heimbecker, Dr. R. B. Salter, Dr. W. R. Harris and Dr. W. J. Horsey. The fellowships awarded the latter two are for research in Canada. These doctors have been selected previously for permanent clinical appointments in teaching hospitals. The fellowships include an adequate family allowance.

Seven years ago a group of parents of children with cerebral palsy organized a clinic at St. Paul's Church. Since then the clinic has grown and has moved to larger quarters. It now has a paid personnel of two physiotherapists, an occupational therapist, a speech therapist, a matron and a directress. A large number of volunteer workers help regularly. This year the Ontario Society for Crippled Children announced a $10,000 annual grant to the clinic.

Nearly 1,000 nurses attended the annual convention of the Registered Nurses' Association of Ontario. There are 23,576 nurses registered in Ontario; more than 12,000 are members of their association. The province has 61 schools of nursing. LILLIAN A. CHASE

QUEBEC

A cobalt bomb of the latest type will be installed in the new wing of the Royal Victoria Hospital in Montreal, which is scheduled for completion in the summer of 1955. This has been made possible by a generous gift to the hospital by Mr. J. W. McConnell. This unit, when finally installed, will be unique in that it will be suspended from the ceiling of the operating room from a sort of movable crane. The six other units now in operation in Canada are stationary. It is believed that the movable unit will assure better control and better positioning for treatment.

This new service will be under the direction of Dr. C. B. Peirce, radiologist in chief; Dr. Jean Bouchard, radiologist in charge of the treatment section; and their staff, including Dr. L. Stephen-Newsham, the radiation physicist who will maintain the new unit.

McGill University medical library, one of the most outstanding on the North American continent and particularly known for its collection of periodicals, will have a medical doctor as full-time librarian for the first time in its 131 year history. Dr. Lloyd G. Stevenson, of the University of Western Ontario, has been appointed librarian of the medical library, assistant librarian of the Osler library and associate professor in the medical faculty. The appointment is effective July 1.

Dr. Stevenson, who served in the RCAMC in the last war, is at present associate professor of medical history and literature at the University of Western Ontario, where he gained both B.A. and M.D. degrees. He also holds a Ph.D. degree from the Institute of History of Medicine, Johns Hopkins University. In 1950 Dr. Stevenson was given a five-year grant by the Markle Foundation.

McGill medical library has had three women librarians in its lengthy history: Miss Margaret Charleton, Miss Jean Cameron and Miss Edith Gordon, the present librarian. They have administered the library under the direction of honorary librarians appointed from the medical faculty staff.

Dr. G. Earle Wight of Montreal has been appointed chief of medical services for the Canadian Pacific Railway. He will carry on in succession to the late Dr. Charles Fenwick. Dr. Wight went overseas with the 9th Canadian Field Ambulance. He was, in fact, the first medical officer to go overseas during the last war. Since the war, he has lectured at McGill University, maintained a large private practice, been associate in medicine at the Montreal General Hospital, and acted as district medical officer with the C.P.R. at Montreal.

The annual clinical evening of the Montreal Medico-Chirurgical Society was held at the Royal Victoria Hospital on April 9. It was unique in that half of the 30 exhibits presented dealt with problems related to the gastro-intestinal tract. The excellent programme for the evening was organized under the direction of Dr. Philip Hill, chairman of the hospital's postgraduate board.

Dr. V. A. Kral, psychiatrist at Verdun Protestant Hospital, reported to the psychiatry section of the same Society on April 22 on prefrontal lobotomy. Their experience goes against previous findings that the operation impairs organization of thought. It does not produce a permanent memory defect and has more influence on the emotions, less on thinking capacity. The procedure calls for careful postoperative nursing, and rehabilitation is begun almost at once after the operation. Most important is an understanding attitude on the part of the family if the patient is to make maximum recovery. Dr. George Reed, the hospital's superintendent, emphasized during the discussion that re-education by occupational therapists and liaison with the home by social service are important factors in this "desperate remedy for desperate cases."

Dr. Walter C. Alvarez of Chicago, editor of the *American Journal of Gastro-Enterology* and the *American Journal of Geriatrics*, addressed the Society at Queen Mary Veterans' Hospital on April 23. He emphasized that a high percentage of patients who come to doctors complaining of stomach disorders are really suffering from emotional problems. The most common disease today is mental illness. He cited the fact that in the United States one out of eight men called in the draft for the armed services is turned down for mental reasons. In his long experience at the Mayo Clinic he has seen many weird symptoms. In many cases, where the general practitioner was not sure what was wrong, the surgeon had looked in vain for trouble in the abdomen. In such situations a talk with the patient in order to try to find out what is bothering him can be most helpful.

The Quebec Division of the Canadian Anæsthetists Society held a one day meeting at the Montreal Children's Memorial Hospital on April 10. About 85 doctors were present and participated in reviewing problems of child anæsthesia. Dr. H. H. Slater, director of the department of anæsthesia at the hospital, said that in the last six years not one death has occurred due to the administration of anæsthetics in the hospital. This was partly due to the introduction of new techniques, drugs, gadgets and machines, and especially to the spirit of co-operation existing in the operating room between nurse, surgeon and anæsthetist.

The official opening of the new physiotherapy department at St. Mary's Hospital in Montreal was held on April 25. Credit for the new centre goes largely to the

Canadian Arthritis and Rheumatism Society which obtained a Federal General Public Health Grant. This money, allocated through the Provincial Health Department, was used for the purchase of ultra-modern equipment. The Arthritis and Rheumatism Society chose St. Mary's Hospital as the most suitable location at which to further the society's services in the city.

Premier Maurice Duplessis announced on May 1 the formation of a special committee charged with the collection of information about hospitals. The members of this committee will visit various sections of the province for the purpose of studying the various local and regional problems in hospital matters. Members of the committee are Dr. Gerald Lasalle of Outremont, Dr. Lucien Larue of Quebec City, and Jack R. Latter, also of Quebec. Acting as advisers will be Dr. Jean Gregoire, Deputy Minister of Health, and Dr. Jean Charles Beaudet, Assistant Deputy Minister of Health.

At the same time the Premier announced that the Quebec government's annual contributions to the hospitals of the province will be increased by $10,000,000. According to this new increased contribution, some hospitals will get a daily allowance of $7.50 per bed instead of $5.50 and others will get $1.80 more for each bed. He added that this initiative on the part of the government has been made possible by the adoption of a provincial income tax.

A. H. NEUFELD

SASKATCHEWAN

From the Swift Current Health Region it has been learned that the 1954 contract for physician services with the Swift Current District Medical Society has been completed. This contract is very similar to the agreement which came into effect in 1953, in that the Regional Board has agreed to guarantee a minimum payment of 75% of the contract schedule of fees as outlined by the College of Physicians and Surgeons of Saskatchewan. A total amount of $460,000 has been budgeted for regional medical care and the District Medical Society has agreed to accept a maximum of 90% of the contract schedule of fees or $460,000 whichever is the lesser. For 1954 the Regional Board has limited their liability on ordinary office calls to $1.00, and on office calls with complete physical examinations to $2.00. This means that the balance of the physician's fees will be paid by the patient.

The Regional Board is continuing to provide out-patient service at hospitals to all residents at no charge. Should a patient wish to have a certain diagnostic procedure done in the doctor's office rather than attend an out-patient department at the hospital the physician may make a charge for these services. Last year there was an increase in the out-patient diagnostic service and as such it is expected that there will be a further increase in 1954.

The imposition of a utilization fee on home calls which went into effect January 1, 1953, resulted in more than a 50% reduction in the number of these calls. Up until August 10 it was noted that there had been a steady increase in office calls and minor surgical procedures. After August 10 when a $1.00 utilization fee was applied to office calls, there appeared to be some decline in their number. As a result of these restrictions the Regional Board will have a surplus at the end of 1953, and for the first time since the inception of the plan, will not be carrying a deficit.

Appointment of a ten-member Advisory Committee on Alcoholism was announced recently by the Honourable J. H. Sturdy, Minister of Social Welfare and Rehabilitation. This committee was established to advise the Government in planning a provincial programme to deal with problem drinking in Saskatchewan. It will work in co-operation with the Bureau on Alcoholism, which was set up last October within the Department of Social Welfare and Rehabilitation with Mr. J. F. A. Calder as director.

Mr. Sturdy said that the committee will survey the problem, present facilities here and elsewhere for helping the victims, and make recommendations to the provincial government concerning future courses of action. One aspect to be studied is the field of prevention, with the prospects of a public information programme and a special education programme in the schools of the Province. The membership of the Advisory Committe represents an extensive cross-section of the people of Saskatchewan. Some of the members are directly concerned with the problem of alcoholism through their professions, while others have been active in a wide range of public service organizations.

A new three-year diploma course in nursing at the University of Saskatchewan at Saskatoon has been announced by the University and the University Hospital. The new course for nurses in training will be directed by the University's School of Nursing, with first classes to start in September. Students in this diploma course will receive board and room without charge in the new nurses' residence on the campus, as well as uniforms and laundry service, plus monthly allowances for each of the three years in attendance. A fee of $50.00 per year will cover tuition, registration, health services and student activities fees. Students will be required to purchase their own textbooks.

A new bi-monthly rehabilitation clinic was opened on February 24 at North Battleford. This clinic financed by the Council for Crippled Children and Adults through the Easter Seal and March of Dimes Fund, is the second such district clinic to be undertaken by the Council. A similar clinic is already held in Prince Albert and plans are now being completed to open additional clinics in Swift Current and Melfort. These regular two day clinics bring a team of therapists, social worker, and psychologist together with the local physicians and medical health officers who check and treat handicapped persons.

A rheumatic fever control project will be conducted in Moose Jaw Health Region No. 6 this spring and summer. This scheme provides for rheumatic fever victims to receive daily administrations of penicillin supplied free through the Provincial Department of Public Health, with the project being financed through a research grant.

During 1952 rheumatic fever and chronic rheumatic heart disease claimed more lives in Saskatchewan than did either polio or tuberculosis, excluding Indians from these statistics, with a total of 1,235 persons admitted to hospital that year with 119 deaths.

A hospital construction grant of $40,000 to assist in renovating the isolation building of the Regina General Hospital has been approved by the Saskatchewan Department of Public Health according to a recent announcement made by the Honourable T. J. Bentley, Minister of Public Health. An application to the federal government for a matching amount under the Federal Hospital Construction Grant is to be made in the near future.

During 1953, the Saskatchewan Air Ambulance Service completed a total of 760 flight requests which involved more than 1700 hours of flying time, covering a total mileage of over 252,000 miles: 119 flights were made involving poliomyelitis patients, 168 to transport accident cases, and 102 flights were made to transport patients suffering from gastro-intestinal ailments.

The two Monagham respirators purchased early in 1953 were used extensively in the transportation of bulbar poliomyelitis victims, while the two new type acclibators were used frequently during the year in the transportation of premature infants.

Increased general revenue to this province will make possible an increase of over 1.5 million in the Health Department budget for 1954-55. This will bring it over twenty million dollars on revenue account. A large portion of this budget will go towards the provision of preventive health services and possibly a new health region. The mental health programme next year will cost 5.8 million, with an additional two million being spent for expansion of mental institutions. Medical services to recipients of pensions and social aid will cost approximately 1.25 million, the Cancer Commission 0.75 million, and grants to the T.B. Sanatorium more than half a million.

With expansion possible this year, the government has decided to give more emphasis to its rehabilitation programme. The budget thus provides for a co-ordinator to work with all agencies involved to tie together more effectively the programmes already in existence. Housing and nursing care for the aged will also receive greater emphasis.

In the past five years, it was recently pointed out, the federal government has made $4,500,000 available for hospital construction in the province, and in addition another $5,500,000 federal fund has been allotted for health purposes apart from the annual federal subsidy under the federal provincial tax rental agreement.

Recently, the Honourable T. J. Bentley stated that Saskatchewan now has 7.2 hospital beds per 1,000 population, the highest ratio on the continent. The Hospital Services Plan, he said, had brought hospitals financial stability. Other advances included free cancer treatment, improved mental health services, and work on the establishment of a medical school, an institution for the mentally retarded, and a programme for the rehabilitation of the disabled.

At the recent annual meeting of the Saskatchewan Division of the Canadian Cancer Society, Dr. F. Hedley Auld retired as provincial president after serving three years in that capacity. Dr. Auld's leadership at the provincial and national levels has been outstanding.

Mr. Justice Doiron steps into the presidency after a period of service which began in 1948. Since his appointment as Provincial Campaign Chairman in 1949 he has led five successive annual campaigns over the top by a wide margin. Through effective organization every third household in Saskatchewan has a supporting member in the Society. His keen interest in the work of the Society and his energy and enthusiasm have been a great source of strength and encouragement. G. W. PEACOCK

NEWS OF THE MEDICAL SERVICES

Canadian Armed Forces

Surgeon Captain E. H. Lee, QHP, Medical Director General, Naval Services visited the Admiralty, London, England and the Senior Naval Liaison Officer Canadian Joint Staff, London during the month of May.

Brigadier K. A. Hunter, OBE, CD, QHP, RCAMC, Director General of Medical Services, visited the 1st Canadian Infantry Brigade Group in Germany and inspected medical units during the month of April and May 1954. While in Europe, Brigadier Hunter visited the Director General Army Medical Services, RAMC and medical establishments in England and on the Continent.

Colonel E. J. Young, CD, has been appointed Assistant Director General of Medical Services, 1 Commonwealth Division, Korea replacing Colonel J. S. McCannel, OBE, who will succeed Colonel Young as Command Medical Officer, Western Command.

During the latter week of March, the Director General of Medical Service's Study Group was held at Camp Borden. It was attended by members of his staff from Army Headquarters, Command and Area Medical Officers, ADsMS Reserve Force, Army medical specialists and consultants to the RCAMC. At the end of the study period, a Mess Dinner was held at which the following trophies were presented to the RCAMC Corps Mess:

1. The Flag of the Republic of Columbia, which was personally presented to Colonel J. E. Andrews, ED, in Japan by the Commander of the Republic Force for special services rendered to him and other casualties of his forces serving in Korea;
2. A portrait of Major (M-in-C) Margaret C. Macdonald, RRC, first Matron-in-Chief, RCAMC at Ottawa during World War I 1914-19, was presented by Major (M-in-C) E. E. Andrews, ARRC, CD, the present Matron-in-Chief;
3. A silver dinner gong from officers of 79 Canadian Field Ambulance while serving in Europe;
4. The Crest of the Armed Forces Medical Service School, US Army, was presented by Colonel J. L. Snyder, MC, LM, BSM. He also presented the mess with the Flag of the Lone Star State.

Air Commodore A. A. G. Corbet, Director of Medical Services (Air) visited RCAF units in the U.K., RCAF Air Division Headquarters, and the four RCAF Fighter Wings in Europe during the month of May.

NEWS AND NOTES

FEDERAL GRANT TOWARDS MANITOBA'S LABORATORY AND DIAGNOSTIC SERVICES

A $55,580 grant under the National Health Program to support extension of laboratory and diagnostic services in Manitoba has been announced. These funds, to be applied to the province's program of improved laboratory and radiological diagnostic services, will assist in purchase of equipment and supplies as well as in the provision of certain necessary additional technical personnel.

It is proposed, among other projects, to have two consultant radiologists, one stationed in Winnipeg, who would give service to Selkirk and Central Manitoba, and one at Brandon, to look after Virden and Hamiota, with possible new units at Neepawa. There will also be consultation available to the provincial mental hospitals in Brandon, Portage and Selkirk. On the laboratory side, the services of a medically-qualified bacteriologist and certain technicians are being added to the Virden regional laboratory service.

ESPANOLA, ONT., HOSPITAL GETS FEDERAL HEALTH GRANT

Grant of $46,444.67 has been made by the federal government, under terms of the National Health Programme, for extension of accommodation at the General Hospital at Espanola, Ont. The funds, to be matched by Ontario, will assist in construction of 33 new active treatment beds, a recovery bed and two labour beds at the Espanola hospital, as well as two nurses' beds and outpatient facilities at the hospital. The new construction thus assisted will increase hospital accommodation in a developing section of Northern Ontario.

ISOLATION OF CASTLE'S INTRINSIC FACTOR

Twenty-five years ago Castle postulated the presence of an "intrinsic factor" in normal gastric juice; deficiency in this factor occurred in pernicious anæmia. Latner *et al.* (*Lancet*, 1: 497, 1954) believe that they have at last isolated the factor in a pure state from gastric juice, and that it is a mucoprotein of molecular weight of the order of 15,000.

NOTICE

The first Canadian Cancer Research Conference will be held at Honey Harbour, Ont., from June 16 to 19 inclusive. This Conference is being sponsored by the National Cancer Institute of Canada, and is primarily designed to encourage a review of present knowledge on various aspects of cancer for the benefit of grantees of the Institute. The topics to be discussed include: Carcinogenesis, Enzyme Relationships, Tumour Host Relations and The Effects of Radiation. Very limited accommodation is possible and attendance must be by application only. Further information may be obtained from Dr. Robert L. Noble, Collip Medical Research Laboratory, University of Western Ontario, London, Ontario, Canada.

The College of Physicians and Surgeons of Ontario at its 89th Annual Session elected the following officers and appointed the following Committees:

President—Dr. J. A. Dauphinee, Toronto; Vice-President—Dr. D. S. Wigle, Windsor, Ont.

Executive Committee—Dr. J. A. Dauphinee, Toronto, (Chairman); Dr. Carl E. Hill, Lansing; Dr. J. H. McPhedran, Toronto; Dr. J. F. Sparks, Kingston; and Dr. D. S. Wigle, Windsor.

Discipline Committee—Dr. F. S. Brien, London, (Chairman); Dr. Malcolm Cameron, Toronto; Dr. J. C. Gillie, Fort William; Dr. G. C. Jarrott, Stratford; and Dr. A. B. Whytock, Niagara Falls.

Education and Registration Committee—Dr. Malcolm Brown, Kingston, (Chairman); Dr. J. F. Argue, Ottawa; Dr. F. S. Brien, London; Dr. A. L. Richard, Ottawa; Dr. J. F. Sparks, Kingston.

Legislation, Advisory, Rules and Regulations Committee—Dr. J. C. Gillie, Fort William, (Chairman); Dr. J. F. Argue, Ottawa; Dr. Malcolm Brown, Kingston; Dr. G. C. Jarrott, Stratford; Dr. J. H. McPhedran, Toronto; Dr. A. B. Whytock, Niagara Falls; Dr. Ward Woolner, Ayr.

Finance, Printing and Property—Dr. Carl E. Hill, Lansing, (Chairman); Dr. Malcolm Cameron; Dr. A. L. Richard; Dr. R. W. Schnarr; Dr. Ward Woolner.

The Henry Simpson Newland Prize in Surgery, established to commemorate the services of Sir Henry Newland to the medical profession, is open for competition.

The Prize will consist of a money award of One Hundred Pounds (£100), together with a medal. The first award will be made in 1955, the subject of the essay being: "The Influence Upon Surgical Practice of Irradiation and Endocrine Therapy." The dissertation should be based on personal observation and experience, and must be typewritten or printed in English. It must not exceed 50,000 words. Essays must be delivered to the General Secretary, Federal Council of the British Medical Association in Australia, 135 Macquarie Street, Sydney, not later than May 20, 1955.

The competition is open to any graduate of any medical school within the British Commonwealth.

(Continued on page 68 of the advertising section)

BOOK REVIEWS

REGENERATION AND WOUND-HEALING

A. E. Needham, University Demonstrator in Zoology, University of Oxford. 152 pp. 8s. 6d. net. Methuen & Co. Ltd., London, W.C. 2, 1952.

This small volume deals with the problem of wound healing at all levels of the animal kingdom. The author has conducted a very thorough search of the physical changes and biochemical events concerned with the problem of regeneration and the result should find ready acceptance by anyone more than casually interested in the subject. It contains an exhaustive bibliography to assist the reader in the pursuit of any particular point of interest.

HYPERTENSIVE DISEASES

H. A. Schroeder, Associate Professor of Medicine and Director, Hypertension Division, Department of Internal Medicine, Washington University School of Medicine; Assistant Physician, Barnes Hospital, Saint Louis, Missouri. 610 pp. illust. $10.00. Lea & Febiger, Philadelphia; The Macmillan Co. of Canada Ltd., Toronto 2, 1953.

This book has been awaited with considerable interest by all those interested in the therapy of hypertension, and it will well repay careful reading. The early chapters are devoted to discussions, necessarily brief but sufficiently comprehensive, on the factors regulating blood pressure, on definitions and on etiological factors such as heredity, environment, the kidney and neurogenic factors. Several chapters deal with clinical and pathological considerations and with specific types of hypertension as in pheochromocytoma. An important chapter discusses the classification, differential diagnosis and investigation. Treatment, particularly with respect to the use of hypotensive agents, notably hexamethonium and apresoline (Hyphex), is laid out in great detail. The results are impressive but the author emphasizes that the problem is by no means solved and that the present approach is only "one small step forward."

CLINICAL PSYCHIATRY FOR PRACTITIONERS AND STUDENTS

I. Skottowe, Psychiatrist, Warneford and Park Hospitals, Oxford. 395 pp., $7.25. Eyre & Spottiswoode, London, W.C. 2; McClelland & Stewart Ltd., Toronto 13, 1953.

This well written and enjoyable book may be called a good example of English electicism and psychobiology. It is subheaded "For Practitioners and Students" and is not meant as a text for those who aspire to specialism. However in spite of this it makes good and provocative reading for the psychiatrist. Dr. Skottowe possesses an elegant and lively style and an atmosphere of genial and humane good sense pervades the book. The absence of those boring and poorly presented case histories whose padded bulk swell so many psychiatric texts calls for commendation. Unless one has a great talent for thumbnail sketches of the extraordinary or a genius that can make even the ordinary notable, it is wise to eschew a method of communication which can only be used by a master of prose. Unhappily most psychiatrists are neither masters of prose nor well informed enough about the technique of writing to avoid this pitfall.

Of course there are and must be many faults which will be remedied in future editions. The matter of certifying insanity has been done inadequately and skimpily. Students and practitioners need clear and proper guidance on the snares of certification and Dr. Skottowe fails to provide this, although he is surely capable of doing so. The least a practitioner can do for a patient is to write an honest, sensible, useful and

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legally unassailable certificate and many fail to do this from sheer ignorance of what is involved in committing a person to a mental hospital.

On page 240 there appears the advice to give continuous narcosis for a period of 8 to 12 weeks. This must be a misprint and yet on page 125 one finds Dr. Skottowe recommending 2 to 3 weeks of 20 hours sleep a day "or even longer". He does not emphasize nearly enough that continuous narcosis is no plaything and has many hazards which rise steadily in the hands of the inexperienced. It would surely be wise to have some advice on treating barbiturate poisoning at the end of the continuous narcosis section? The section on treatment of toxic confusional states is inadequate and pays too little attention to the work of Gould and others who have achieved excellent results with infusions of glucose, adequate fluids and massive doses of vitamins.

However in spite of criticism this is a full flavoured book which will be read with equal pleasure by the experienced and inexperienced, to savour the wise and witty words of one who is clearly a first class doctor.

CLINICAL INVESTIGATION

E. H. Stokes, Senior Honorary Physician, Sydney Hospital; Honorary Lecturer in Medicine and Lecturer in Clinical Medicine, University of Sydney. 628 pp. illust. £5/5/-. Angus and Robertson Ltd., Sydney, 1953.

This textbook should have a different title. It deals with history taking, physical diagnosis and laboratory examination of urine and blood. On this continent and in England, too, clinical investigation has come to mean much more than the description of signs and symptoms and routine laboratory methods. It embraces the basic sciences of physiology, biochemistry, pharmacology, bacteriology, etc., in their application to the study of human disease. Clinical investigation is much more than diagnosis; it is a discipline by which the mechanism of disease processes are brought to light, new methods in diagnosis discovered, the action of drugs at the bedside understood, all for the improvement of treatment. It is therefore unfortunate that the title is misleading, unintentional though it may be. As a manual of diagnosis designed for students and practitioners it is excellent and should take its rightful place in this class of textbook. It is highly recommended for those for whom it was written.

THE MANAGEMENT OF ABDOMINAL OPERATIONS

Edited by R. Maingot. 1253 pp. illust. $24.00. The Macmillan Co. of Canada Ltd., Toronto, 1953.

With the expansion of other surgical specialties, particularly that of cardiovascular surgery, many have regarded the abdominal surgery as a closed chapter. This new edition confirms clearly that it is not. In the words of the editor, the "Management" is defined as "artful, ingenious methods of treatment". With that objective, a wide variety of contribution to the book seems to emphasize the physiopathological and metabolic problems in gastrointestinal surgery. New data, available from clinical and experimental investigations on surgical shock, fluid and electrolyte balance, the role of vitamins, are ably correlated, with special reference to abdominal cases.

The reader finds two particularly valuable features in the book: (1) The understanding of ways in which recent advances in antibiotics, blood transfusion and anæsthesia affect not only the mortality rates in abdominal operations, but also the technique of surgical approach, making operative intervention possible in cases previously left to conservative treatment. (2) The way of presentation of controversial problems of etiology and treatment, in which the decision is left to the reader. A good example of this approach is the discussion of the dumping syndrome. After a concise description of confirmed data, the author discusses the mechanical, chemical and psychosomatic factors of the syndrome, without offering dogmatic conclusion. The book, written on a postgraduate level, is not only a valuable aid in surgical studies, but also a potential stimulus for anyone interested in the ever-expanding field of gastroenterology.

CLINICAL ORTHOPÆDICS

Edited by A. F. DePalma, Editor-in-Chief. Number One, 242 pp. illust., single copy, $6.00. or sustaining orders $5.00 each. J. B. Lippincott Company, Montreal, 1953.

This publication is divided into two parts, the first dealing with a specific topic, and the second containing articles on miscellaneous topics related to and concerned with orthopædic surgery, but also of interest and concern to the general practitioner and those in allied specialties. The problems pertaining to children's orthopædics are presented concisely and completely, covering a wide range of topics from arthritis through congenital and traumatic disorders, to be concluded by a discussion on tuberculosis of the spine in children. The articles on arthritis and Perthes' disease deserve special mention for their information, presentation and advice.

Under the heading of General Orthopædics the introduction relating to research is particularly timely and should be read especially by men undergoing training at the present time. The articles following are all extremely readable and instructive. The journal as a whole is a credit to the editors and the various authors. If subsequent volumes come up to the excellence of the first number, Clinical Orthopædics should be an unqualified success.

TEXTBOOK OF MEDICAL TREATMENT

Edited by D. M. Dunlop, Professor of Therapeutics and Clinical Medicine, University of Edinburgh; L. S. P. Davidson, Physician, H. M. The Queen in Scotland; Professor of Medicine and Clinical Medicine, University of Edinburgh; and Sir J. McNee, Physician, H. M. The Queen in Scotland; Regius Professor of Practice of Medicine, University of Glasgow. 1023 pp. illust. 6th ed. $9.50. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Ltd., Toronto 2, 1953.

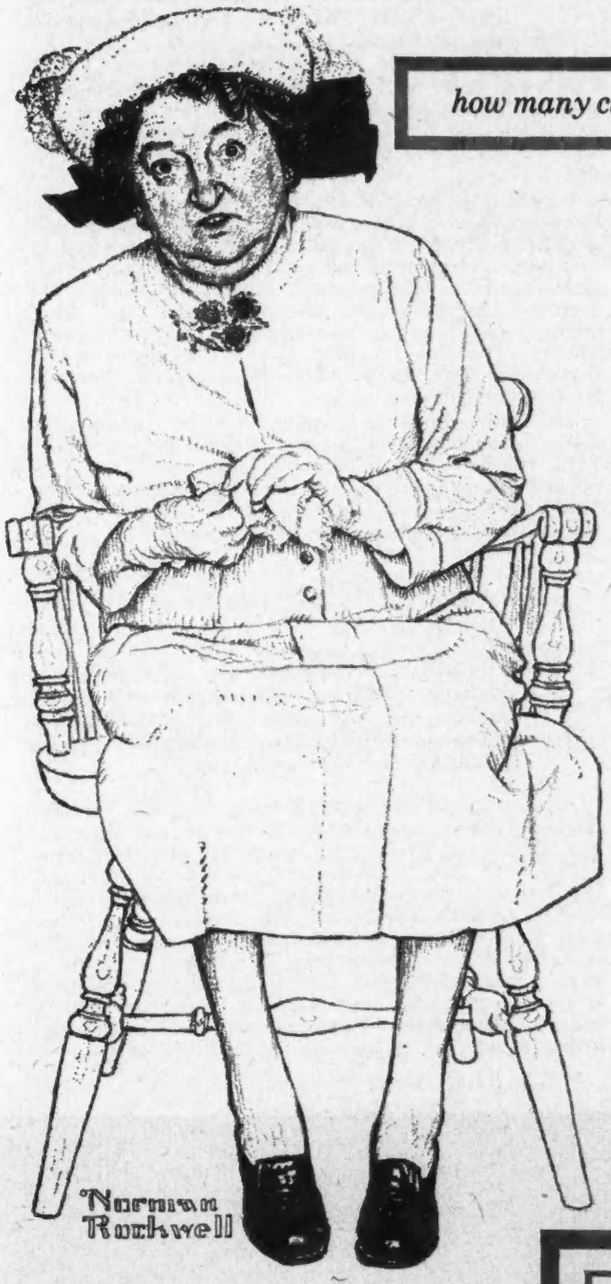
This completely revised sixth edition of a familiar work is a welcome successor to the previous editions. New chapters have been added. These deal with chemotherapy, rehabilitation, the treatment of poisoning, and chemotherapy of malignant disease.

The subject of medical therapeutics is presented in a sensible way. The eminent authors have selected for detailed description, methods found to be most useful in their own experience. This considerable volume is a manual of immense value to student and practitioner alike.

PATHOLOGY OF THE HEART

Edited by S. E. Gould, Clinical Professor of Pathology, Wayne University College of Medicine, Detroit, Michigan; Pathologist, Wayne County General Hospital, Eloise, Michigan. 1023 pp. illust. $28.00. Charles C. Thomas, Springfield, Illinois; The Ryerson Press, Toronto, 1953.

A most comprehensive textbook on the heart has been drawn together by the editor and authors. They deal first with the history of its pathological disorders, its anatomy and embryology and normal and abnormal



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physiology and then with the pathological aspects of its diseases. A considerable time is devoted to congenital malformations, to be followed by chapters on the degenerative conditions, vascular disturbances, rheumatic and non-rheumatic inflammatory diseases, parasitic, neoplastic and traumatic disorders of the heart. There is an excellent chapter on clinicopathologic correlations and finally an appendix with tables of standard weights and measurements and a detailed description of the methods of pathological examination of the heart, including the injection of coronary arteries. The bibliography is a most extensive one and the numerous illustrations are mainly well-conceived and technically-excellent photographs of actual gross and microscopic preparations. The diagrammatic representations are relatively few in number.

The scope of this book is vast and it may be highly commended as a reference work and as a textbook for, not only pathologists, but all those who are interested in or deal with the clinical manifestations of heart disease. The clinical aspects and implications in heart disease are repeatedly introduced in relation to the pathological features. Controversial subjects, such as the etiology of calcific aortic valve stenosis are amply dealt with, and one can find in this book most of the known facts in relation to the pathology of diseases of the heart.

MAN'S BACK

T. A. Willis, Formerly Head, Department of Orthopædic Surgery, St. Luke's Hospital; Consulting Orthopædic Surgeon, U.S.P.H.S. Hospital, Cleveland, Ohio. 161 pp. illust. $10.50. Charles C. Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1953.

This short volume deals with the many conditions of the human back. The author has tried to cover most of the problems to varying degree, without any effort being made that this work be an omnibus. However, it is because of this that the reviewer finds fault. The information offered is a little more than that usually possessed by the non-orthopædic surgeon. It is difficult to understand for whom the book is truly intended. It is of little value to the orthopædic surgeon. To the others, the possession of the information offered may lure the recipient into a false sense of security—that this is all that is to be known about a man's back. It is a concise book, easy to read, with illustrations that are moderately good.

The volume is to be read at one's leisure. However, it cannot be recommended, other than to students who desire a little more than is in the general textbook of orthopædics.

PAIN SYNDROMES AND THEIR TREATMENT

J. M. Tarsy, Chief, Arthritis Clinic, University (New York Postgraduate) Hospital, New York University-Bellevue Medical Centre. 592 pp. illust. $13.25. Charles C. Thomas, Springfield, Illinois; The Ryerson Press, Toronto, 1953.

This work deals with the pain syndromes involving the shoulder region and upper extremity. Part I covers the anatomical and physiological bases for these syndromes and the description of the various methods of examination.

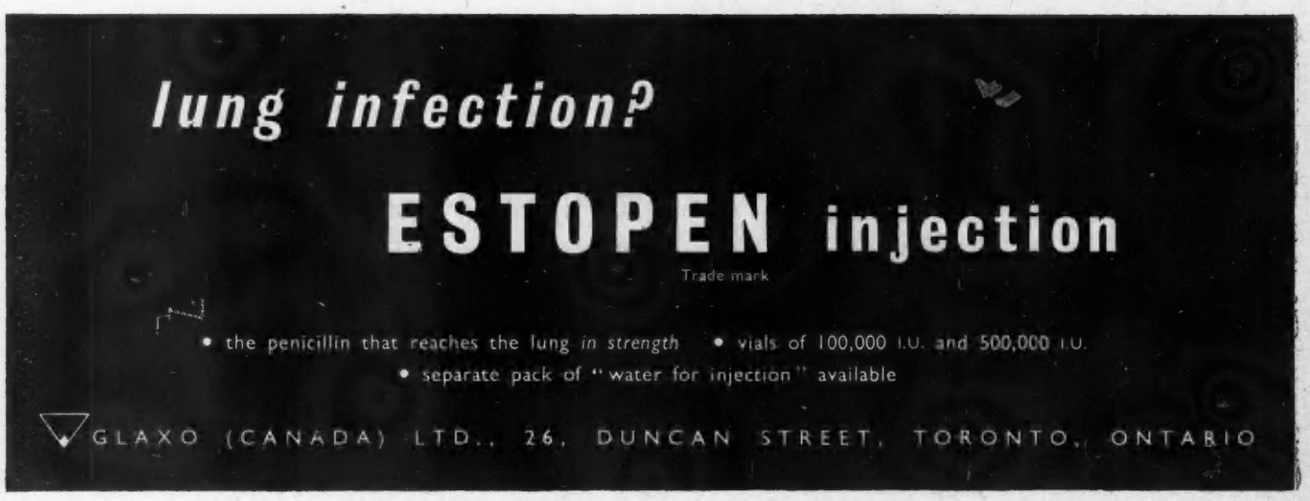
Parts II, III, IV, and V describe the pain syndromes in cervical lesions, thoracic lesions, shoulder lesions, and peripheral lesions respectively. Part VI is devoted to treatment. Here the different local analgesic techniques including heat, manipulation, immobilization, traction, exercises, Roentgen- and electro-therapies, and therapeutic nerve block are described for the various syndromes. The final chapter details the procedures of therapeutic nerve block. There is an excellent and extensive bibliography.

The author is to be congratulated on gathering together so much material on this difficult field of knowledge. His work will be valued chiefly by the rheumatologist and orthopædist, who should possess this volume. Many physicians and practitioners will find this a valuable source of reference.

DISC LESIONS FOR THE GENERAL PRACTITIONER

J. Cyriax, Physician to the Department of Physical Medicine, St. Thomas's Hospital, London. 37 pp. illust. $1.00. Cassell and Company Ltd., London; British Book Service (Canada) Ltd., Toronto 6, 1953.

In this pamphlet the etiology and diagnosis of disc disease and the various forms of therapy are discussed. The general practitioner, for whom the pamphlet is intended, will find it interesting although controversial. Dr. Cyriax maintains that there is little place for laminectomy in cervical and thoracic disc disease except where there is pressure on the spinal cord. He also feels that laminectomy should be avoided in lumbar lesions unless gross lumbar deformity, foot drop, bladder symptoms or recurrent attacks have occurred. Particular stress is laid on manipulation measures, but unfortunately the reader is referred to journals for precise details.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CLINICAL ENDOCRINOLOGY

K. E. Paschkis, Associate Professor of Medicine, Director of the Division of Endocrine and Cancer Research, Jefferson Medical College; A. E. Rakoff, Clinical Professor of Obstetric and Gynæcologic Endocrinology, Jefferson Medical College; and A. Cantarow, Professor of Biochemistry, Jefferson Medical College, 830 pp. illust. $16.00. Paul B. Hoeber, Inc., New York 16, 1954.

This is the latest of a number of new books on endocrinology which have appeared since World War II. Although "clinical" is suitably applied in the title, the authors deal thoroughly with the anatomy, embryology, and physiology of each endocrine gland. There are numerous illustrations and diagrams which serve to clarify the text. A section on Laboratory Methods is included providing a useful rapid reference to the tests which may be of value in a particular patient. There are several minor points with which this reviewer would take issue. The use of parathyroid hormone in the management of hypoparathyroidism as recommended, has largely been supplanted by the oral use of A.T. 10, which is here relegated to a secondary role. The section on acute thyroiditis does not mention the use of x-ray therapy or cortisone, both having been found useful in a disease which, though self-limited, may be prolonged and distressingly painful.

The authors have chosen to exclude largely discussion of the use of hormones in non-endocrine disease, except for a brief and incomplete list of diseases treated with ACTH and cortisone. The use of hormones in palliation of cancer is not described.

The book will be useful to students and doctors alike. It is authoritative and well written.

WILLIAM CHESELDEN 1688 - 1752

Sir Zachary Cope, Consulting Surgeon to St. Mary's Hospital, Paddington. 112 pp. illust. $3.40. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Ltd., Toronto 2, 1953.

This monograph in the straightforward style that would have pleased his contemporaries does honour to the chief representative of English surgery in the first half of the eighteenth century. The "ingenious Mr. Cheselden" has somehow been crowded out of the spotlight of medical history by the more famous Hunters who were his contemporaries, and it is therefore pleasing that Sir Zachary Cope has revived the figure of the man who was eminent in an age of great men and whose achievements in anatomy, in operative surgery and in establishing the position of surgery gave strength and distinction to British medicine and are landmarks in the history of the profession as a whole.

The author does full justice to these achievements, places Cheselden the surgeon and man of the world imaginatively in the vigorous life of his time, and paints a most compelling picture of a large-minded, tolerant and gifted physician. The chapter on Cheselden and his friends is particularly well done. The illustrations are of unusual interest. The book as a whole reflects great credit on the publishers. Certainly in volumes such as this the muse of medical history is being handsomely served in our time which may yet be known to posterity as an age of fine historical writing.

COPYING AND DUPLICATING MEDICAL SUBJECTS AND RADIOGRAPHS

H. L. Gibson, Technical Editor, Eastman Kodak Company, Rochester, N.Y. 75 pp. illust. $5.50. Charles C. Thomas, Springfield, Illinois; The Ryerson Press, Toronto, 1953.

Though intended primarily for doctors who prepare their own photographic records and for other amateur photographers, this book will serve as a useful summary for the trained medical photographer.

The inexperienced photographer will learn to make the best use of simple equipment by taking specific preparatory steps and precautions. Only in the chapter on the copying of radiographs, a subject more complex than is usually appreciated, does the author limit his discussion to one type of equipment. But even in this field basic principles are given which will allow each photographer to experiment with his own equipment. The tables of specific procedures and of film and exposure data are eminently practical. The instructions for copying black-and-white originals, coloured originals in black-and-white and colour, and motion picture frames and colour transparencies in black-and-white for publication can make the difference between crude and finished results.

The format is convenient and pleasing, the print large and the language untechnical whenever possible. The illustrations of procedures and the examples of results are well chosen and of excellent quality.

DISEASES OF THE EYE

A Textbook for Students and Practitioners. E. Wolff, Surgeon, Moorfields Westminster and Central Eye Hospital; Ophthalmic Surgeon, Royal Northern Hospital. 224 pp. illust., 4th ed. $6.00. Cassell & Co., Ltd., London; British Book Service (Canada) Ltd., Toronto, 1953.

In the title the author states this book is for students and practitioners and it is written with this aim in mind. Diseases of the eye are presented in a concise and orderly fashion. The more common conditions with which one meets in practice are well presented and discussed. The uncommon conditions are relegated to small type. The illustrations are excellent, showing both the clinical and pathological changes seen in disease. Many of the illustrations are taken from the author's other books. The chapter on ophthalmic operations is covered in a superficial manner and gives only an indication of what is done at these operations. The appendix covers the use of the newer drugs which are of use in ophthalmic practice. In the present day so many new drugs are brought out that it is impossible to give a complete list in a book of this type. In the section discussing "retrolental fibroplasia", the author's theories have been outdated by recent findings in the etiology of this disease.

Taken as a whole, this book is a valuable addition to the library of the practitioner and the student. The ophthalmic problems which are met clinically are clearly presented and proper treatment is discussed. The excellent illustrations speak volumes by themselves.

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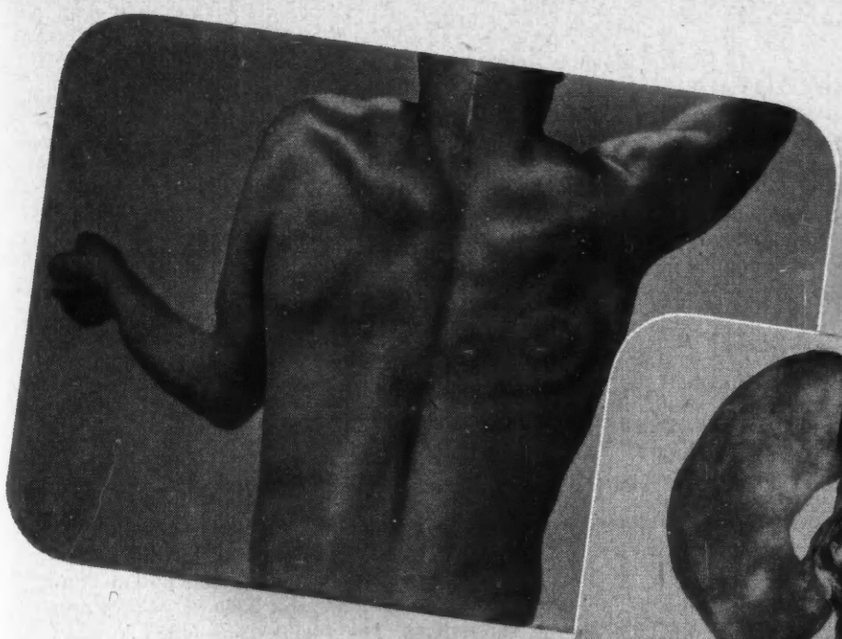
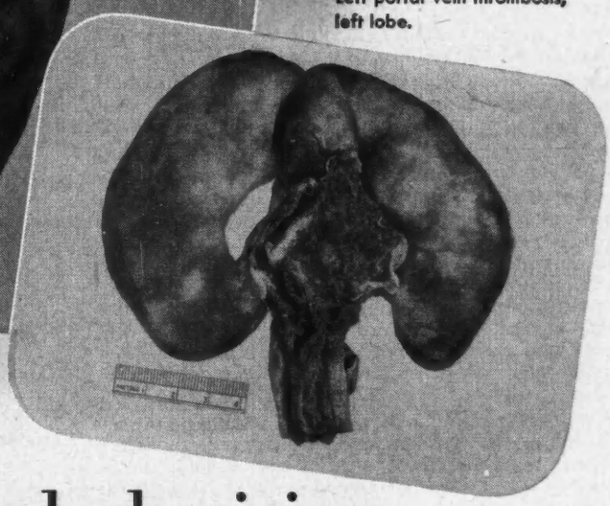


Amyotrophic lateral sclerosis.



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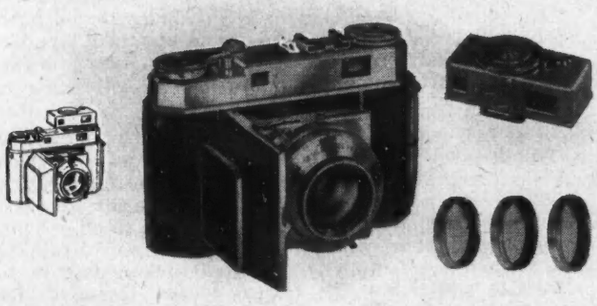

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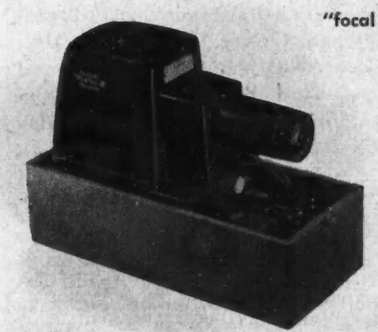

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Canad. M. A. J.
June 1954, vol. 70

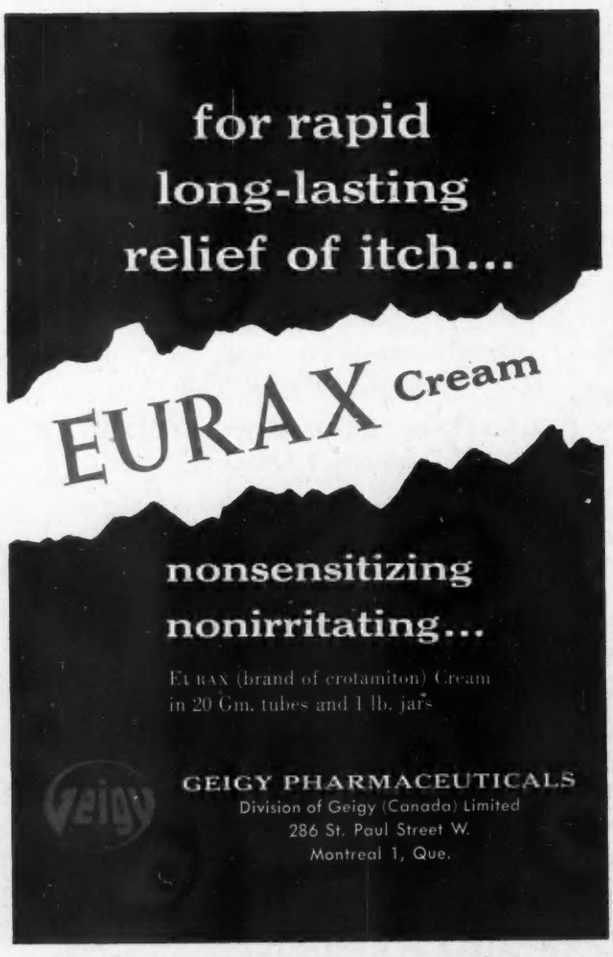
OFFICIAL HISTORY OF THE CANADIAN MEDICAL SERVICES 1939-1945. CLINICAL SUBJECTS

Edited by W. R. Feasby, Lieutenant-Colonel, R.C.A.M.C., Supplementary Reserve, Lecturer in Physiology, University of Toronto. Vol. II, 537 pp. illust. $5.00. Queen's Printer and Controller of Stationery, Ottawa, 1953.

This long-expected volume, dealing with clinical subjects, has now been published. Volume I, dealing with the administrative aspects of the Canadian Medical Services in World War II, will it is hoped be published shortly. Volume II is unique in that it tells in a single volume the clinical experience of the three Canadian Medical Services, and therefore gives one the opportunity to compare their procedures and results. The first twenty-six chapters deal with clinical problems encountered during the process of mobilization and fighting. The material is presented by individuals who had responsibilities in carrying out treatment policy. It is a historical presentation. Some of the authors have, however, emphasized lessons which were learned, together with appropriate recommendations. In general, the story has been told of the work of all the specialties that were active during the war.

Chapters 27 to 31 deal with the medical research done in the three Services and in supporting civilian institutions. Some of these studies are dealt with in considerable detail. The last chapters of the book deal with medical statistics—a summary of medical experiences during the war. It is unfortunate that statistics during the early part of the war left much to be desired. For this reason, no doubt, a good deal of interesting information of this period was not recorded, constituting a definite loss. On the whole, the records given should stimulate a good deal of thought and study.

This volume, published by the Queen's Printer, is attractively put together. Most of the chapters present a fair summary of experience in the three Services with the subject under discussion. No doubt space limitation is the reason for curtailment or omission of some material of considerable interest. Every Canadian doctor, whether or not he served in one of the armed forces, will wish to have this book on his shelf.



THE PLURIPOTENCY OF THE HYPOPHYSEAL HORMONES.

J. Samuels, Specialist for endogenous endocrinotherapy, Director of the Central Institution for the Samuels-Therapy, Amsterdam. 296 pp. illust. Price 37 guilders. Ed. N. V. Cycloscoop, Amsterdam, The Netherlands, 1953.

The author of this extraordinary book believes that all benign and malignant tumours are caused by hyperfunction of gonadotrophic or thyrotrophic centres respectively. By "spectroscopic means" he claims to be able to tell "in less than 30 seconds" whether or not a person is suffering from either form of "pituitary dysfunction." Such a pituitary, gonadal or thyroid dysfunction can be treated by "short wave radiation" of the appropriate glands. The claim is made that not a single patient has been lost who has continued such treatment regularly (often three times a week!). He admits, however, that no microscopic evidence of tumour disappearance is available as "one never finds a patient whose tumour has ceased further growth who will agree to biopsy!"

This book is difficult to read. This is partly because it is a translation, and partly because of the way in which it has been written. Statements are made dogmatically without details of any supporting experiments; the text is broken by long paragraphs of references to other published works of recognized authorities alleged to support his thesis; generalizations are often so sweeping as to frustrate and annoy the critical reader. Probably few endocrinologists will accept the ideas in the form in which they are expressed, but nevertheless, the book is a stimulating one. It is perhaps of interest, too, to remember that hypophysectomy is today being advocated by reputable surgeons for advanced carcinoma.

PROBLEMS OF FERTILITY IN GENERAL PRACTICE

J. Stallworthy, Obstetrician and Gynæcologist, Radcliffe Infirmary, Oxford; Examiner in Midwifery and Gynæcology, Oxford University; and others. 259 pp. illust. $4.00. Cassell and Co. Ltd., London; British Book Service (Canada) Ltd., Toronto, 1953.

The title of this small book is somewhat misleading. It deals with problems of fertility, clinical contraception and a brief summary of the problems of eugenics in clinical practice. Its approach to all these problems is practical, non-controversial and, therefore, should be very useful to the practising physician. These subjects have not been generally well covered in the average gynæcological text and its greatest value to both general practitioner and specialist is that they are discussed under one cover.

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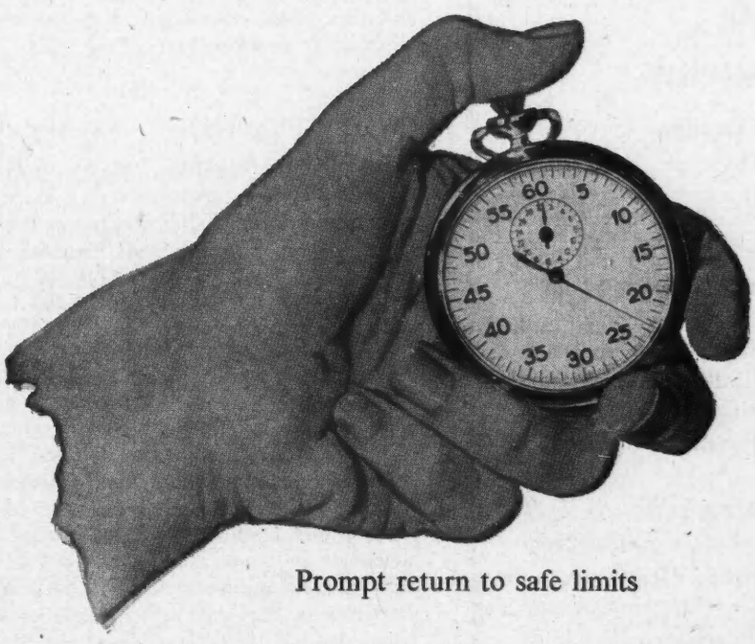

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TEXTBOOK OF PATHOLOGY

W. Boyd, Professor of Pathology, University of British Columbia, Vancouver, B.C. 1024 pp. illust., 6th ed. $12.50. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Ltd., Toronto 2, 1953.

This is a new edition of a text which has been a favourite for over twenty years. The old text has been thoroughly revised and much new material added. Completely new material includes the influence of cortisone on inflammation and healing; the concept of field of influence in relation to repair; epidemic hæmorrhagic fever; Guillain-Barré syndrome; and a complete chapter on skin. The re-written sections include gangrene; syphilis; the radiosensitivity of tumours; nephrosis, and the anæmias. The book is completely up-to-date and presents all the essential material in a form which is easy to read and to assimilate. While not a complete reference book, it is highly recommended for students, graduate or undergraduate.

THE DIABETIC NEUROPATHIES

J. I. Goodman, Senior Clinical Instructor, Western Reserve University; Senior Visiting Physician and Physician in Charge of Diabetic Clinic, Mount Sinai Hospital; and others. 138 pp. illust. $5.25. Charles C. Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1953.

This monograph reviews the literature on the neurological complications seen in diabetes. The authors add their own series of patients and comment on the supposed etiological factors: they discuss the arguments both for and against arteriosclerotic changes and vitamin deficiencies as a cause for diabetic neuropathy. Their conclusion in regard to pathogenesis is: "the cause lies in some as yet obscure metabolic change in nerve tissue incidental to uncontrolled diabetes." In discussing the differential diagnosis, the authors refer to lead affecting primarily the motor nerves: it has been known for some years that, in fact, lead does not affect the nerves primarily, but that lead palsy is due to a deposition of lead in the muscles. The book will be of some interest not only to those specializing in diabetes but to internists and general practitioners.

METHODS OF EXAMINATION IN EAR, NOSE AND THROAT

W. G. Scott-Brown, Ear, Nose and Throat Surgeon, Royal Free Hospital, London. 110 pp. illust. $3.75. Butterworth & Co. (Canada) Ltd., Toronto, 1954.

This small book may be recommended to the medical student, the general practitioner and the pædiatrician. It describes clearly, simply and in detail all the commonly used methods of clinical examination of the ear, nose, pharynx and larynx. The investigation of vestibular function by caloric stimulation as well as the various means of testing hearing are well described in the sections on the vestibular and cochlear apparatus. In addition, practical information is included on x-ray techniques in relation to the paranasal sinuses and mastoid structures. The book is generously illustrated throughout with diagrams and x-ray plates.

Books Received

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

You and Your Skin. N. R. Goldsmith, Dermatologist, St. Joseph's Hospital, Lancaster, Pa. 148 pp. illust. $4.25. Charles C. Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1953.

Plague. R. Pollitzer, formerly of the Division of Epidemiological and Health Statistical Services, World Health Organization. 698 pp. Illust. Clothbound: £3 5s, $10.00, Sw. fr. 40; Paperbound: £3, $9.00, Sw. fr. 36. World Health Organization, Geneva, 1954.

Exerimental Surgery. J. Markowitz, Associate Professor of Physiology, University of Toronto; Visiting Professor of Physiology, Ontario Veterinary College, Guelph. 851 pp. Illust. 3rd ed. $10.00. The Williams & Wilkins Company, Baltimore; Burns & MacEachern, Toronto 2, 1954.

Hope and Help in Parkinson's Disease. J. C. Button, Jr., Neurologist, Elizabeth (N.J.) Memorial Hospital and North Jersey Osteopathic General Hospital; Director, Button Neurological Institute. 198 pp. Vantage Press, Inc., New York; Burns & MacEachern, Toronto 5, 1953.

The Cyclopedia of Medicine, Surgery, Specialties. Editor-in-Chief: G. M. Piersol, Professor of Medicine and Director of the Centre for Research and Instruction in Physical Medicine, Graduate School of Medicine, and Professor of Physical Medicine, School of Medicine, University of Pennsylvania. Assistant editor: E. L. Bortz, Associate Profesor of Medicine, Graduate school of Medicine, University of Pennsylvania. In 15 volumes, including index volume. 14,460 pp. Illust. 3rd ed. Cloth, loose-leaf. $195.00. F. A. Davis, Philadelphia; The Ryerson Press, Toronto, 1953.

Energy Metabolism and Nutrition. R. W. Swift and C. E. French, Department of Animal Nutrition, The Pennsylvania, State University. 264 pp. Illust. $5.75. The Scarecrow Press, Washington, D.C., 1954.

Problems of Consciousness. Edited by H. A. Abramson, Assistant Professor of Physiology, Columbia University College of Physicians and Surgeons, New York, 177 pp. $3.25. Josiah Macy, Jr. Foundation, New York, 1954.

The Billroth I Gastric Resection. H. G. Moore, formerly Instructor in Surgery, University of Washington School of Medicine; and H. N. Harkins, Professor of Surgery and Executive Officer of the Department of Surgery, University of Washington School of Medicine. 175 pp. Illust. $7.50. Little, Brown and Company, Toronto, 1954.

Map: World Distribution of Rickettsial Diseases—Tick-Borne and Mite-Borne Forms. Plate II. $1.25. Department of Medical Geography, American Geographical Society, New York 32, 1954.

Betty Lee. C. D. Tucker. 168 pp. $3.00. The Macmillan Co. of Canada Ltd., Toronto, 1954.

The Head and Neck. W. H. Hollinshead, Professor of Anatomy, Mayo Foundation, University of Minnesota; Head of the Section of Anatomy, Mayo Clinic, Rochester, Minn. 560 pp. Illust. Vol. 1. $12.00. Paul B. Hoeber, Inc., New York 16, 1954.

French's Index of Differential Diagnosis. A. H. Douthwaite, Senior Physician, Guy's Hospital; Honorary Physician, All Saints' Hospital for Genito-urinary Diseases. 1,046 pp. Illust. 7th ed. $18.00. John Wright & Sons Ltd., Bristol; The Macmillan Company of Canada, Toronto, 1954.

Practical Electrocardiography. H. J. L. Marriott, Associate Professor of Medicine, University of Maryland; Assistant Cardiologist, Mercy Hospital, Baltimore. 170 pp. Illust. $5.00. The Williams & Wilkins Company, Baltimore; Burns & MacEachern, Toronto 2, 1954.

Psychology, The Nurse and the Patient. D. M. Odlum, Senior Psychiatrist, Elizabeth Garrett Anderson Hospital, Consultant Psychotherapist, West End Hospital for Nervous Diseases, London. 168 pp. 2nd ed. 12/6d. Nursing Mirror Publication, London; Philosophical Library, New York 16, 1954.

Proceedings of the Society for the Study of Fertility. Liverpool Conference 1953, 104 pp. Illust. 10/-. W. Heffer & Sons Ltd., Cambridge, England.

Tuberculosis in Childhood and Adolescence. F. J. Bentley, Senior Physician; S. Grzybowski, Senior Registrar, High Wood Hospital for Children, Brentwood, Essex; and B. Benjamin, Formerly Statistician, London County Council. 259 pp. Illust. $5.00. National Association for the Prevention of Tuberculosis, London, 1954.

A Doctor's Case Book. P. Tournier. 250 pp. $3.25. SCM Press Ltd., London; The Ryerson Press, Toronto, 1954.

Lectures on the Thyroid. J. H. Means, Jackson Professor of Clinical Medicine Emeritus, Harvard University; Former Chief of Medical Services, Massachusetts General Hospital; Physician, Massachusetts Institute of Technology. 112 pp. Illust. $3.30. Harvard University Press, Cambridge; S. J. Reginald Saunders & Co., Ltd., Toronto, 1954.

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Manuscripts must be typewritten, double spaced, and the original copy.

Papers should be kept below 4,000 words wherever possible. Whilst not necessarily a cause for rejection, excessive length of an article is undesirable.

References: in the case of a journal arrange as follows: author (JONES, A. B.), title, journal, volume, page, year. In the case of a book: WILSON, A., Practice of Medicine, Macmillan, London, 1st ed., p. 120, 1922.

Illustrations: A limited number will be accepted. Photographs should be clear: drawings should be in india ink on white paper. All unmounted. Legends to be typed separately.

Reprints: May be ordered upon forms sent with galley proofs.

News: The Editor will be glad to consider any items of news that may be sent in by readers.

The Royal College of Physicians and Surgeons of Canada

ANNOUNCEMENT OF EXAMINATIONS

Examinations are held for the Fellowship in Medicine and the Fellowship in Surgery, and for the Certificate in the approved medical and surgical specialties.

The lists for the 1954 Examinations are now closed, but applications for the 1955 Examinations will be received until **April 30, 1955.**

Regulations and Requirements of Graduate Training relating to the Examinations, as revised May 1951, application forms, lists of approved hospitals in Canada, and assessment of training application forms, may be obtained from:

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If a box number is requested, there will be an additional charge of 50c on the first advertisement to cover postage and handling charges.

NOTICE.—THE B.C. CIVIL SERVICE REQUIRES PSYCHIATRISTS FOR BRITISH COLUMBIA MENTAL HEALTH SERVICES.—The British Columbia Mental Health Services invite applications from qualified psychiatrists for staff positions at the Crease Clinic and Provincial Mental Hospital, Essondale. Applicants must be licensed by the Medical Council of Canada and be eligible for licensing by the College of Physicians and Surgeons of British Columbia and they must be certified in Psychiatry by the Royal College of Physicians and Surgeons (Canada) or equivalent. Permanent appointment is available to British subjects under the age of 45 except that veterans are accepted over the age of 45. The following salary range applies over a five year period: $576.00 — $596.00 — $620.00 — $644.00 — $668.00. There is a sound superannuation plan in operation and generous vacation and sick leave privileges. For further information and application forms communicate with Director, Provincial Mental Health Services, Crease Clinic, Essondale, B.C. or the B.C. Civil Service Commission, Weiler Building, Victoria, B.C.

NOTICE.—Splendid opening for general or specialized private practice on North Yonge St. Toronto, near Steeles Avenue, in a community of now approximately three thousand and constantly growing. Excellent office space available July 1st; also convenient housing accommodation if desired. The development of a Health Centre here a possibility. Reply to Box 932, Canadian Medical Association Journal, 3640 University Street, Montreal, Que.

WANTED TO BUY.—Certified surgeon, McGill graduate, Protestant, age 46, desires to buy surgical practice in Vancouver, or seeks opening in partnership or assistantship with other busy surgeon. Would consider other surgical practices for sale in British Columbia. Reply to Box 925, Canadian Medical Association Journal, 3640 University Street, Montreal, Que.

FOR RENT.—Doctor's office, 3 rooms suite, common furnish waiting room, professional building, Guy and Sherbrooke location. Write to Dr. M. Eidinger, Suite 32, 3465 Côte des Neiges Road, Montreal, Que., or telephone WEllington 8273.

FOR RENT.—In modern building, new five room, completely adequate medical suite. Located in new, expanding east end of Hamilton, Ont. Reply to Box 923, Canadian Medical Association Journal, 3640 University Street, Montreal, Que.

FOR SALE.—Private practice in south eastern Saskatchewan town. New 6 room office, fully modern for nominal rent. Sell for cost of complete equipment: x-ray, frigidaire, speed-clave, instruments, etc. $4,000, half cash. Modern hospital 17 miles. Possession arranged. Reply to Box 948, Canadian Medical Association Journal, 3640 University Street, Montreal, Que.

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(Continued on page 36)

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From the Journal of June 1924

The Venereal Diseases Grant

"It is not yet known whether the Dominion Government grant to the Provinces for the treatment and control of venereal diseases is to stand intact during the coming year. Rumour has it that $50,000 is to be cut from the grant, and that possibly the following year the grant will be discontinued. The reasons given for attacking this grant are the necessity for economy, and the statement that the grant itself is unconstitutional, as under the British North America Act the provinces are supposed to look after health matters themselves.

"In opposition to this we desire to emphasize the fact that in 1919 a definite decision was arrived at for the establishment of a Dominion Department of Health and a Dominion-wide health programme. Anything that would undermine the influence and importance of this Federal Department is greatly to be regretted. The profession earnestly hopes that the present Government will not lessen the amount devoted to this department and by so doing abandon work that has thus far been carried on successfully and economically and has proved to be of great value and importance to the whole of the Dominion."

A Lister Memorial

"Acting upon the suggestion of Dr. John Stewart of Halifax, a former student and assistant of Lister, the Association decided two years ago to establish a Triennial Oration in honour of Lister. A committee was appointed to study the question; and as the result of their deliberations it has been decided through the pages of the Journal to ask the members of the Association for contributions towards the establishment of a fund for this object. The sum considered necessary is $5,000. The interest on this would amount to about $750 in three years. An Oration, celebrating the memory of Lord Lister to be delivered triennially before the Canadian Medical Association at its annual meeting will require about that sum for defraying the expenses incurred.

"It may be stated that already some $600 has been subscribed. The Journal would urge a careful consideration of this project on the part of its readers. There must be few indeed who, realizing what Lister has meant to medical science in general and to the fame, in the medical world, of our Empire in particular, will not desire to have their names in the list of those who propose to perpetuate in honour his name in this part of the world. It is a real pride of possession. Dr. John Stewart is to deliver the first Listerian Oration at the coming meeting in Ottawa".

Nova Scotia News

"Arrangements for a two weeks' course for graduates under the auspices of the Dalhousie Faculty of Medicine, have been practically completed. This will commence on September 1. A particularly attractive programme has been prepared. The mornings will be given up almost entirely to operative and other clinics, conducted by members of the Dalhousie Faculty. The afternoons will be given over to eminent teachers from other colleges. Sir Henry Grey, Drs. W. W. Chipman and L. J. Rhea, of Montreal, and Dr. R. D. Rudolf, of Toronto, have very kindly consented to give three lectures each, and Drs. Luther MacKenzie and Ross Faulkner, of New York, will also contribute to the course. Halifax offers many attractions to visitors in September, so the late afternoon and evening hours are left open for recreation. The course is offered without charge to all medical men. Dr. H. K. MacDonald is chairman of the committee, and Dr. W. Alan Curry is secretary."

Quebec News

"The new Notre Dame Hospital on Sherbrooke Street East is rapidly being completed and is expected to be ready for patients very shortly. It is a handsome building with a frontage of 400 feet and a depth of 230 feet, and faces Lafontaine Park thus assuring abundance of fresh air. This property was the gift of the late Sir Rodolphe Forget who gave it as a hospital site some twenty years ago. Dr. O. F. Mercier is the Medical Superintendent.

"The Rev. Canon Allan P. Shatford, Grand Master of the Freemasons of Quebec, formally laid the corner stone of the Shriners Hospital for Crippled Children to be erected immediately adjacent to the Children's Memorial Hospital on the southern slope of the mountain. This hospital will be one of a chain of similar institutions now built, or being built, throughout the continent by the Nobles of the Mystic Shrine, an auxiliary of the Masonic order responsible for the alleviation of distress, suffering and want among those unable to help themselves. It is estimated that the hospital will cost between $400,000 and $500,000."

Ontario News

"Hospital Day was celebrated in London, Ontario on May 12, and each of the seven institutions there reported a large number of interested visitors and well wishers. The Minister of Health, Honourable Dr. Forbes Godfrey, visited the different institutions at various times through the day, and made the announcement at the Institution of Public Health that he hoped to be able to reduce the cost of insulin from a cent and a half to one cent per unit."

British Columbia News

"Mr. C. J. Fletcher, the Executive Secretary of the B.C. Medical Association, has just completed a tour through the Okanagan and Kootenay Districts, and a second trip to Victoria, visiting every doctor individually and bringing him up-to-date with the activities of the Association. These visits appear to be greatly appreciated, especially by the country doctors who, otherwise, would not be able to keep in touch with things. Membership fees were paid with alacrity, and the opinion freely expressed that the Association, whilst yet comparatively a young organization, was destined to become indispensable to the interests of the profession. It is realized that the membership fee is somewhat high, and it is hoped to make some modification next year."

Automobile Emblems

"During the past year the Committee in Charge of Federal Legislative Bureau of the Association has been studying the question of Group Insurance for members of the Association. In this connection it was considered advisable that a distinct Association Emblem for automobiles should be available, the advantage being evident, especially during the Association's meetings. Designs were prepared and submitted to the Executive at the March meeting. The design which met with approval is now being lithographed in colours and copies will be distributed to members in order to determine the number desired. Steps have been taken to protect the design by a "trade-mark". Tenders have been invited from manufacturers in different centres. Naturally the price varies according to the size of the initial order. Distribution will be effected through the Secretary's Office."

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NEWS AND NOTES

(Continued from page 713)

PROVIDE FEDERAL FUNDS FOR HEALTH RESEARCH IN QUEBEC

Approval of federal support under the National Health Programme for additional health research in Quebec is announced. Sums totalling more than $16,000 will be provided under the Programme's Public Health Research Grant to projects recommended for federal contributions by Quebec health authorities.

A grant of $4,700 will be made to the Sanatorium St. Joseph de Rosemont, Montreal, in connection with studies related to protein alteration in serum and red blood corpuscles in tuberculosis. A grant of $6,710 will support the Department of Obstetrics and Gynæcology, McGill University, in investigating the resuscitation of new-born babies, especially the premature, in order to cut down complications and to reduce fetal mortality. This study will relate to active reviving of the infant at birth and also to the management of the first few days of life, as well as to oxygen therapy and chemical studies with regard to oxygen intake and carbon dioxide output. It will consider modern methods in this field and also estimate the value of oxygen and other drugs in saving small babies.

Another grant of $2,600 goes to the Institute of Microbiology and Hygiene, University of Montreal, to help develop a rapid method for determination of an antitubercular substance, and the Department of Bacteriology and Immunology of McGill University is assisted in the sum of $2,300 in studies of pathogenic fungi.

FEDERAL HEALTH GRANTS SUPPORT QUEBEC MEDICAL RESEARCH WORK

Further federal assistance to medical research in Quebec has been provided in the form of grants valued at more than $55,000 under the terms of the National Health Programme. Approval has been given to a federal contribution, through the Programme's Public Health Grant, of $44,720 to support research being carried on at McGill University, Montreal, on the basic causes of hypersensitivity, with special reference to non-tuberculous allergic disease of the chest. This study promises to provide valuable information, primarily in the field of allergy, but with possible unlimited relation to the whole field of disease.

Another federal contribution provides $8,000, through the Mental Health Grant, to a Montreal Neurological Institute investigation related to the analysis of the mechanism of epileptic discharge, with a view to gaining greater insight into the fundamental mechanism of epileptic disorders of cerebral function and of the functional significance of the electrical activity of the brain.

A Public Health Research Grant of $3,000 has been approved for studies in the Institute of Microbiology and Hygiene, University of Montreal, concerning "the influence of lipotropic and antilipotropic factors on the lipids of mycobacteria".

VICTORIA HOSPITAL QUALIFIES FOR FEDERAL HEALTH GRANT

An addition to the psychopathic unit of Royal Jubilee Hospital, Victoria, B.C., has qualified for a federal grant under terms of the National Health Programme. A grant of $12,772.50, approved under the Programme's Hospital Construction Grant, will assist British Columbia in increasing accommodation at the Royal Jubilee Hospital.

In applying for federal aid, British Columbia health authorities submitted that the new addition would provide an additional eight active treatment beds and added clinical areas, which will be used for in-patients and out-patients. The minister noted that new construction will make available an occupational therapy department, medical (psychiatric) clinic and a recreational and diversional therapy department.

CANADIAN INTERNATIONAL TRADE FAIR

This year's Canadian International Trade Fair promises to be a more interesting, better balanced show than ever before. Twenty-six countries are so far represented with exhibits, and the products listed for display range from ceramics and handicrafts to machine tools and power plants. Almost every one of the 22 trade classifications into which the Fair is divided contains a substantial variety of products from a number of countries.

Canada is the leading exhibiting country, with 125,000 square feet out of a total of 224,000 square feet booked to date. Other major exhibiting countries are: the United Kingdom, Germany, the United States, Italy, Belgium, Austria, India and France.

Medical and Optical Instruments.

The precision medical and optical instruments group will be represented at the Trade Fair this year by exhibitors from Italy, Germany, Canada, and the United Kingdom, with Italy the leading exhibiting country.

Italy is showing metallographic and toolmakers' microscopes, as well as analytical microscopes and other items, including hardness testers. Canadian firms are showing specialized precision instruments, production and inspection equipment and photographic equipment. A British firm is displaying optical tools, surveying transits, high speed drills, reamers and cutters, which will also have a place in the Scientific Equipment section.

FEDERAL HEALTH GRANT FOR CHICOUTIMI, QUE. HOSPITAL

A federal hospital construction grant of $30,000 is being made to Quebec, under terms of the National Health Programme, to assist in providing nursing accommodation at Hotel Dieu St. Vallier Hospital, Chicoutimi, Que. The grant will contribute to the cost of 60 nurses' beds, to be added to the Chicoutimi hospital, providing accommodation for nurses in training.

The appointment of Dr. Kenneth B. Babcock of Detroit as director of the Joint Commission on Accreditation of Hospitals has been announced.

Dr. Babcock succeeds Dr. Edwin L. Crosby, newly-appointed executive director of the American Hospital Association.

The Joint Commission is an independent group voluntarily supported by five leading health agencies in the United States and Canada to improve hospital care by establishing certain standards and by accrediting the hospitals which request survey and meet such standards. Its headquarters are in Chicago. It is supported by the American College of Physicians, American College of Surgeons, American Hospital Association, American Medical Association and the Canadian Medical Association. It was organized in 1951 to take over the hospital accrediting programme from the American College of Surgeons which had conducted the programme since 1918. Last year, its first year of actual operation of the programme, the Commission fully accredited 2,920 hospitals and gave provisional accreditation to 498 hospitals.

The Commission's surveyors, all physicians, travel throughout the United States, its territories and Canada, to determine whether or not hospitals which request accreditation meet the standards. The Commission publishes an annual list of accredited hospitals, the latest being published in March.

(Continued on page 70 of the advertising section)

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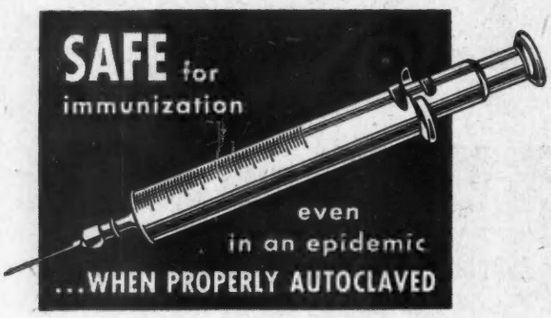

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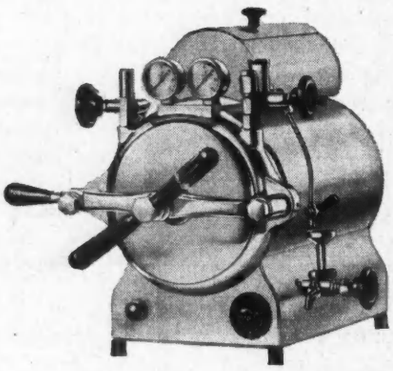

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NEWS AND NOTES

(Continued from page 68 of the advertising section)

In announcing Dr. Babcock's appointment, Dr. Philpott, Chairman of the Commission, said: "We are delighted that Dr. Babcock has accepted the important task of directing the Joint Commission on Accreditation of Hospitals. There is perhaps no more vital programme than this effort by doctors and by hospitals to elevate hospital care standards constantly by a vigorous and voluntary method of self-discipline. Dr. Babcock's career, first as a physician and surgeon and then as a hospital administrator, guarantees the sound continuance of this programme which got off to such an excellent start."

BIG FEDERAL HEALTH GRANT FOR VICTORIA HOSPITAL, LONDON, ONT.

One of the largest federal contributions in some time for extension of hospital facilities in Canada has been announced in the form of a grant of $400,000 to Victoria Hospital, London, Ont. This grant is made under terms of the National Health Programme, the federal measure designed to extend and strengthen the country's health facilities and services.

The Victoria Hospital is increasing its accommodation by 376 active treatment beds and 76 bassinets in cubicles. It is constructing a modern six floor and basement extension, which is expected to be completed shortly. The grant will assist in providing a much needed extension of treatment facilities.

The following comment is made by Dr. Elliott P. Joslin in the first issue of the *News Bulletin* of the International Diabetes Association:

For the moment I can think of nothing more encouraging than the fact that last week (in February, 1954) we gave a Gold Medal to Mrs. Dow, because she had lived twice as long as she was expected to live when she acquired diabetes. Mrs. Dow was in her 99th year and knits and sews and reads and votes, and she was enthusiastically received by the audience when she rose to accept the medal, and was obviously greatly pleased. I wonder if she is the oldest living diabetic in the world.

Great discoveries I am sure will appear in diabetes in 1954, and this is borne in upon me from the evidences I receive from so many countries of a reawakening of an interest in the disease. However great as these may be and indebted as we all are to those who make them, the fact remains that upon every diabetic rests responsibility. Therefore, I am submitting the most recent statistics which we have acquired, and if you should compare them with earlier tables, you would find that never before has the longevity of diabetics in our group, based upon fatal cases, been as great.

STATISTICS JOSLIN CLINIC (1950-1953)
(Compiled by the Statistical Department of The Metropolitan Life Insurance Company)

DURATION OF LIFE SUBSEQUENT TO ONSET OF DIABETES

Age groups at onset	*Number of cases*	*Duration—years*
All	1,358	16.3
0 - 9	46	21.3
10 - 19	92	19.9
20 - 39	212	22.2
40 - 59	667	16.9
60 - over	340	9.7
unknown	1	...

DRUGS IN INFANTILE GASTROENTERITIS

Serious doubt is cast on the value of administering sulphonamides and antibiotics in infantile gastroenteritis by some studies made in the Children's Clinic of the University of Helsinki (*Ann. Med. Int. Fenn.*, **42**: 1, 1953). The author treated 85 cases in four unselected groups. One group received no specific drug therapy, one was given a sulphonamide, one streptomycin and one chloramphenicol. Duration of stay in hospital was taken as the criterion of efficacy of treatment; in this respect, there was no difference between the four groups. This statement was also true of the 75 cases in which an apparently causative microorganism was found in the stools.

FACTORS ASSOCIATED WITH CANCER OF THE BREAST

From an analysis of 949 cases of carcinoma of the breast in Dutch women, it would seem that the risk of this disease is significantly lowered by childbearing. The findings in this series, compared with 239 cases of death from diseases other than carcinoma of the breast, showed that 25% of the breasts affected by carcinoma also had diffuse cystic fibroadenomatosis, as against only 9% in the controls. It seems that: (a) carcinoma is two and a half times as common in breasts the seat of diffuse (not localized) fibroadenomatosis; (b) diffuse cystic fibroadenomatosis leads to cancer only in 4% of cases. Both conditions are commoner in nulliparæ. Once a woman has had one child, the risk of carcinoma is not further reduced by subsequent pregnancies. Celibacy does not appear to affect the statistics.—Straub, M. and Lubbers, E. J. C.: *Ned. Tijdschr. Geneesk.*, **98**: 756, 1954.

FEDERAL SUPPORT FOR HALIFAX CHILD MENTAL HEALTH CLINIC

Nova Scotia will receive federal aid in operating a Mental Health Clinic for Children at Halifax. Approval has been given, under terms of the National Health Programme to a Mental Health Grant of $14,400 to assist in staffing the clinic, which is to incorporate the old Child Guidance Clinic operated by Dalhousie University. The federal grant will assist with salaries for a full-time psychologist and full-time social worker, as well as a part-time psychologist, a part-time social worker, and a part-time secretary.

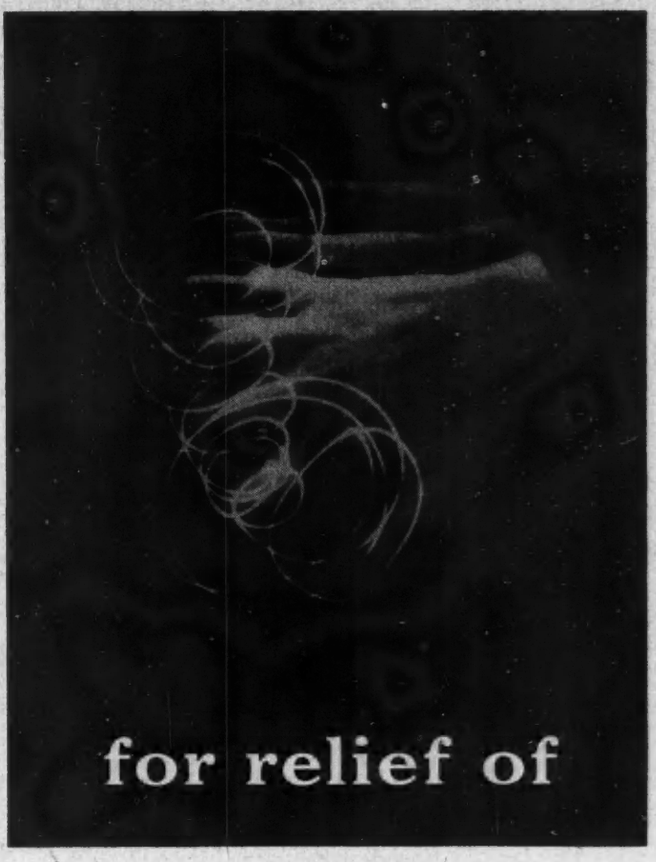
Further assistance has been given to Nova Scotia under the National Health Programme by a grant of $3,000 to enable the province to train a prospective administrative assistant for the Nova Scotia Sanatorium. The appointee is being given a course in Hospital Administration and business procedure at University of Toronto.

NEW BRUNSWICK RECEIVES FEDERAL HEALTH GRANTS

Grants totalling more than $25,000 are being made by the federal government under the National Health Programme to assist further in strengthening health services in New Brunswick.

A General Public Health Grant of $13,237.05 has been approved on recommendation of New Brunswick health authorities in connection with the purchase of x-ray equipment to improve and extend the province's x-ray services. Much of the equipment will be set up at the Victoria Public Hospital, Fredericton, with some at St. Joseph's Hospital, Dalhousie, N.B.

A federal General Public Health Grant of $7,600 will provide bursaries to assist the province in training pathologists for provincial services.



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MORE FEDERAL SUPPORT FOR ONTARIO MEDICAL RESEARCH

Further federal grants of more than $44,000 to assist medical research in Ontario are announced. These include contributions under terms of the National Health Programme to support highly technical investigations in Toronto medical research laboratories. A Public Health Research Grant of $13,940 will go to assist the Connaught Medical Research Laboratories, University of Toronto, with a study of poliomyelitis viruses, in an attempt to establish types of viruses in the eggs of certain species of birds and in some species of animals, by feeding experiments. The Connaught Laboratories are also assisted, under the Public Health Research Grant with $8,000 for another polio virus study aimed at improving strains for production of a vaccine, $6,925 for research in furtherance of the development of a preventive polio vaccine, $3,220 for an electrophoretic study of viruses and $3,580 for the cultivation of treponema pallidum.

Other grants to Ontario research work include $7,600 for a study at the Department of Hygiene and Preventive Medicine, University of Toronto, of diphtheria and tetanus toxoids, looking to the preparation of a purer toxoid for use in immunization, and $750 to the School of Hygiene, University of Toronto, in connection with its search for a simple, economic method for use in the home for removal of nitrate in drinking water, to render it safe for bottle-fed infants. The last-noted contribution is made under the Child and Maternal Health Grant.

MONGOLISM

Mothers who have given birth to a mongol frequently ask what the chance of having another one is. A series of 196 Austrian families in which a mongol had been born was studied, with particular reference to subsequent pregnancies. After giving birth to a mongol 49 of the 196 women had a total of 63 pregnancies. Of these seven ended in abortion, and of the remaining 56 pregnancies, three ended in the birth of a second mongol and the other 53 in birth of a normal child. There is thus a 93% probability that the next child born after a mongol will be normal. In another series collected by Oliver the probability was put at 86%.—Thalhammer, O., *Wien. Klin. Wchschr.*, **66**: 165, 1954.

TREATMENT BEFORE DIAGNOSIS

In the *British Journal of Venereal Diseases* (**30**: 7, 1954) there is an account of an interesting debate on the advisability of giving abortive treatment for the venereal diseases before diagnosis. The proposer of the motion, Dr. R. R. Willcox, based his case to some extent on the World Health Organization mass campaigns against treponematoses in Haiti, Indonesia, Yugoslavia and elsewhere, in which indiscriminate treatment of a whole population had been necessary to eradicate a widespread treponemal infection. Taking also the analogy of suppressive treatment of malaria, and such procedures as the use of the "antibiotic umbrella" at chest operations, he defended treatment before diagnosis in the case of consorts of infectious syphilitics, in females with suspected gonorrhœa, and in individuals exposed to risk.

His brother venereologists, led by Dr. Ambrose King, were in the main reluctant to accept Dr. Willcox's arguments, feeling that the aphorism "diagnosis before treatment" was still fundamentally sound and conjuring up unpleasant visions of a mass descent on English villages with a door-to-door offer of protection against venereal disease. They were doubtful of the curative effects of such abortive treatment as the handing out of oral penicillin tablets before exposure, considered that the risk of causing mass anxiety reactions was enormous, and likened the whole procedure to sheep-dipping, implying that the best insurance against venereal disease was still for the sheep to remain aloof from the goats.

A GIANT BABY

A woman of average size and with average pelvic measurements has given birth in the District Obstetric Clinic, Wuppertal, Elberfeld, Germany to a female infant weighing 7.5 kg. (sixteen and a half pounds).

Apart from the fact that the mother sustained a third-degree tear and that there was difficulty in extracting the shoulders after easy delivery of the head, there was nothing unusual about the labour which lasted only 3½ hours (2-para mother). The infant took six months to recover its birth weight and is now of normal weight for its age. The mother later developed diabetes. Pregnancy had not gone beyond the expected term. It is claimed that this is the largest infant ever spontaneously delivered, and that delivery was probably helped by saddle block anæsthesia.—Dolff, C., *Geburts. u. Frauenheilk.*, **14**: 272, 1954.

SALICYLATES IN RHEUMATIC FEVER

In spite of the volume of literature on salicylate therapy of rheumatic fever, scientific studies of the value of such therapy are few and far between. Now that disappointment with the newer hormone treatment of this disease is again focusing attention on salicylates, the interim report by Professor Illingworth and his associates from Sheffield, England, of a controlled study begun in 1948 (*Quart. J. Med.*, **23**: 177, 1954) assumes considerable importance. These authors, who used salicylates in a dosage of 0.1 gm. per lb. body weight daily, found evidence that children treated with salicylates did better than controls. Temperature and erythrocyte sedimentation rate fell more rapidly in the salicylate group, arthritis settled down faster and there were fewer relapses of the disease or of its joint manifestations. It also seemed that the salicylate group escaped with less cardiac damage, and that benefit was derived from the treatment even when it was started late. The authors point out that they still cannot say what dosage of salicylate is needed or for how long it should be given. They can make no statement about the value of the low dosage generally used in domiciliary treatment, but they feel that the toxic complications encountered with the dosage they employed rule this technique out for general practice without constant supervision and biochemical assistance.

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